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(54) Cylosporin synthetase.

(57) The nucleotide sequence which codes for cyclosporin synthetase and similar enzymes and recombinant vectors containing the sequence. The vectors are used in methods for the production of cyclosporin and cyclosporin derivatives.

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This invention relates to nucleotide sequences which code for enzymes possessing cyclosporin synthetase-like activity and to methods for the production of cyclosporin and cyclosporin derivatives using these sequences.

The fungus *Tolypocladium niveum* (previously known as *Tolypocladium inflatum* GAMS) produces cyclosporins, a group of neutral cyclic peptides composed of eleven amino acids. Other fungi have been found which may form cyclosporins (Dreyfuss, 1986; Nakajima *et al.*, 1989) but *Tolypocladium niveum* is the most important organism for the production of cyclosporins by fermentation. Cyclosporins exhibit remarkable biological effects: for example cyclosporin A, the main metabolite, is a potent immunosuppressant (Borel *et al.*, 1976). An enzyme has been identified which catalyses the entire peptide biosynthesis of cyclosporin and is therefore called cyclosporin synthetase (Zocher *et al.*, 1986, Billich and Zocher 1987). The biosynthesis proceeds non-ribosomally by a thiotemplate process, as has also been described for other peptide synthetases (Kleinkauf and von Döhren 1990). Each amino acid is first activated in the form of an adenylate, then bound in the form of a thioester and linked with the following amino acid to the peptide. In the case of cyclosporin A, seven of the amino acids, bound as thioesters, are methylated before they are linked to the preceding amino acid in a peptide bond. This methylation function is an integral constituent of the enzyme polypeptide (Lawen and Zocher 1990). Including the cyclisation reaction, cyclosporin synthetase performs at least 40 reactions.

Cyclosporin A contains three non-proteinogenic amino acids: D-alanine in position 8, α-amino butyric acid in position 2 and, in position 1, the unusual amino acid (4R)-4-[(E)-2- butenyl]-4-methyl-L-threonine (Bmt or C9 amino acid). All three amino acids must be each prepared by a biosynthetic pathway which is independent of the primary biosynthetic pathway. Cyclosporin synthetase does not possess an alanine-racemase function (Kleinkauf and von Döhren 1990) and thus, D-alanine cannot be produced by cyclosporin synthetase by epimerisation of enzyme-bound L-alanine, as is the case for other peptide antibiotics whose biosynthesis mechanism is known.

Although attempts have been made to isolate and characterize cyclosporin synthetase in terms of its amino acid sequence, because of the complexity and size of the enzyme this has not to date been possible. Hence it has not been possible to characterize the DNA coding for cyclosporin synthetase.

This invention provides a nucleotide sequence which codes for an enzyme possessing cyclosporin synthetase-like activity. In the present specification, an enzyme possessing cyclosporin synthetase-like activity is an enzyme which catalyses the peptide biosynthesis of cyclosporins and structurally related peptides and derivatives.

Preferably, the nucleotide sequence codes for cyclosporin synthetase or an enzyme which is at least 70% (for example, at least 80, 90 or 95%) homologous to it and which possesses cyclosporin synthetase-like activity .

Preferably, the nucleotide sequence codes for an enzyme which possesses cyclosporin synthetase-like activity and in which at least one amino acid recognition unit is different from that of cyclosporin synthetase.

Preferably, the nucleotide sequence comprises the sequence represented in Seq Id 1 or a sequence which hybridises to it under conditions of reduced stringency or, more preferably stringent coinditions. Stringent conditions include hybridisation at 42°C in 6 x SSPE, 50% formamide, 5 x Denhardt's solution, and 0.1% SDS and washing three times for 10 minutes in 2 x SSC, 0.1% SDS and twice for 30 minutes in 0.2 x SSC, 0.1% SDS at 65°C. Reduced stringency conditions include a washing temperature of 60°C. Even more preferably the nucleotide sequence codes for an enzyme having the amino acid sequence set out in Seq Id 2. The nucleotide sequence may have a restriction map as represented in figure 1.

In another aspect, the invention provides a recombinant vector containing a nucleotide sequence as defined above. The vector may include the endogenous promotor for cyclosporin synthetase or may include some other suitable promotor. A suitable promotor region is illustrated in Seq Id 7. The recombinant vector may be in the form of a plasmid, a cosmid, a P1-vector or a YAC-vector. The invention also extends to host cells carrying the vector. Preferably the host cell is a Tolypocladium niveum cell.

The invention also provides a process for the production of cyclosporin or a cyclosporin derivative, comprising cultivating a host cell as defined above and causing the host cell to produce the cyclosporin or cyclosporin derivative.

The invention also provides a method for the production of a cyclosporin derivative, comprising altering the DNA sequence coding for cyclosporin synthetase so that the enzyme causes the production of the cyclosporin derivative, placing the altered DNA sequence in a vector, transforming a host cell with the vector, and causing the host cell to produce the cyclosporin derivative. Preferably the DNA sequence coding for cyclosporin synthetase is altered by changing the fragments that code for amino acid recognition units. Alterations may be made using standard techniques such as those based on PCR procedures. Point deletions, mutations and insertions, as well as larger alterations are possible .

This specification describes the isolation and characterisation of the gene for cyclosporin synthetase from

Tolypocladium niveum and the use of the gene in genetically ngineering cells, including *Tolypocladium niveum* cells. Whil a protocol for the isolati n of cyclosporin synth tase from *Tolypocladium niveum* was published in 1990 (Law n and Zocher 1990), it is howev r not suitabl for extracting larg quantities f homog neous enzyme in a sh rt period of tim . Also, in the publicati n, the synth tase was attributed an M_r f approximately 650,000 Dalt n. It may, h w v r, justifiably be assumed from sedim ntati n analyses with flu rescence-labelled protein (Lawen *et al.*, 1992) and by extrapolation from the protein size of comparable enzymes that cyclosporin synthetase has an M_r of approximately 1,500 kDa. The enzyme occurs as a single polypeptide chain and cannot be decomposed into subunits by either denaturing or reducing agents (Lawen and Zocher 1990).

The enormous size of the enzyme means that a strategy for amino acid sequencing which differs from the customarily used route must be used. Substantially more homogeneous material is required than is generally used to perform fragmentation tests. It is for this reason that a protocol was developed for cyclosporin synthetase which may, in principle, also be applied to analogous enzymes from other microorganisms and, in the practical example of the purification of the enzyme from *Tolypocladium niveum* (example 1), gave rise to a substantial improvement in terms of yield and the amount of time required.

Purification may initially proceed according to customary processes. Cell disruption may be performed, for example, with a high pressure homogeniser or a glass bead mill; the cells being present in moist or lyophilised state. If the cells are moist, pressure disruption is conveniently performed, for example with a Maunton Gaulin apparatus. Lyophilised cells are conveniently broken up by grinding in a mortar under liquid nitrogen.

The crude extract so obtained is clarified by centrifugation. The nucleic acids are removed by precipitating them from the extract using customary reagents for this purpose; polyethyleneimine or protamine sulphate are, for example, used. The nucleic acid precipitation also removes fine suspended particles, which can disturb subsequent purification stages. Then the proteins may be precipitated out of the clarified crude extract to provide the enzyme in a more concentrated form. The protein precipitation is customarily performed with ammonium sulphate. For cyclosporin synthetase, saturation to 50% is sufficient to achieve almost complete precipitation. After this step, the enzyme is in an enriched and highly concentrated state.

In principle, all chromatographic methods are suitable for further purification of the enzyme, such as ion-exchange chromatography and gel permeation chromatography. With very large proteins, gel permeation chromatography is particularly suitable as a very selective purification step. If the correct molecular sieve is chosen, an approximately 90% homogeneous protein preparation may be obtained in a single step. Analysis of purity is performed in SDS polyacrylamide gels (preferably gradient gels 4-15%).

The purification process used produces stable, at least 90% homogeneous, active enzyme preparations, as is necessary for characterisation of enzyme kinetics or protein chemistry. In Example 1, the protocol described in detail for *Tolypocladium niveum,* in comparison with the published method, reduces the time required from 4 days to 10 hours and increases the yield by approximately a factor of 4.

With a protein of this exceptional size, the requirement for amino acid sequences to identify the gene or gene product correctly is naturally greater than for an average-sized protein. Apart from the possibility of N-terminal blocking, it is also not possible to prepare a protein of this size in such a way that it is suitable for N-terminal sequencing. For these reasons, it is necessary to obtain a sufficient number of internal amino acid sequences.

However, when a protein of this size is fragmented, so many fragments are produced (theoretically approximately 700, assuming one cleavage every 20 amino acids) that the standard method of completely fragmenting the protein and purifying the fragments by high-pressure reversed-phase chromatography (HP-RPC) is not practicable. For this reason, fragmentation is performed under conditions which are sub-optimal for the relevant endoproteinases to give substantially larger fragments.

Cyclosporin synthetase is cleaved by adjusting the pH value. In particular, cleavage into large fragments of up to 200 kDa is achieved by adjusting the pH value to approximately 7.5 in a HEPES buffer with the addition of EDTA and DTT. The fragments obtained in this manner may be isolated and enriched as is conventional, for example by using chromatography and electrophoresis, such as the combination of anion exchange chromatography on MonoQ with HP-RPC or the combination of MonoQ with SDS-polyacrylamide gel electrophoresis/electroblot.

The sub-optimal conditions are principally obtained by altering the buffer conditions, and possibly also altering the cleavage temperature (see Example 3 as a possible variant). The nonetheless numerous fragments must each be isolated or enriched by 2 purification steps, it being in principle possible to use any chromatographic and electrophoretic separation techniques. In the case of cyclosporin synthetase fragments from *Tolypocladium niveum,* th c mbinations f ani n xchang chromatography n M noQ with HP-RPC (Examples 4 and 5) and M noQ with SDS-polyacrylamid gel lectrophoresis/electrobl t (Examples 4 and 6) prove particularly advantageous.

The n n-ribosomal biosynthetic pathway implies that the sequenc of th cyclic peptid is determined by

the c rresponding arrangement of the amino acid activating domains. Each of these domains must perform analogous reactions, nam ly th activation of the amin acid by ad nylation and binding in th form of a thioester. H nce it may b xpected that recurr nt, preserv d moieties will be f und in the prot in sequence.

In fact, in previously analysed peptid synthetases, preserved regi ns within the sequences have been discov red, the number f which coincid s with the numb r of amin acids t be activated: three f r ACV synthetase (activates aminoadipic acid, cysteine and valine; Smith *et al.*, 1990, MacCabe *et al.*, 1991, Gutierrez *et al.*, 1991); one each for gramicidine synthetase I (Kraetzschmar *et al.*, 1989) and tyrocidine synthetase I (Weckermann *et al.*, 1988); and four preserved regions in gramicidine synthetase 2, which activates the amino acids proline, valine, ornithine and leucine (Turgay *et al.*, 1992).

Maximally accurate identification and characterisation of such preserved regions of cyclosporin synthetase at both the enzymatic and genetic levels constitutes the basis for well-directed genetic engineering in terms of altering enzyme specificity for the *in vivo* production of cyclosporin variants. It is therefore useful to identify proteolytic fragments of cyclosporin synthetase which may be correlated with a partial function of the synthetase. The following correlations were made:

(1) a protein fragment with a methyl transferase function (the method on which this work is based is, in principle, applicable to all methyl transferases and is published in Yu *et al.*, 1983; a first application to cyclosporin synthetase is published in Lawen and Zocher 1990); see Example 7;

(2) a protein fragment capable of activating L-alanine (Example 8).

The method used in Example 8 exploits the fact that when proteins are subjected to limited proteolytic cleavage, *inter alia* intact domains are cleaved which, due to their correct spatial folding, are still capable of exercising their enzyme function to a limited extent. Theoretically, therefore, each amino acid activating domain may be identified with this method. The optimal conditions (for proteolytic cleavage and its timing in relation to amino acid activation) must, however, be determined by testing in each individual case. Moreover, unambiguous identification of a domain may be achieved only if the amino acid it activates occurs only once in the product.

The gene is isolated by DNA hybridisation with oligonucleotides specific to cyclosporin synthetase (Example 10). Whether a specific DNA fragment actually belongs to the cyclosporin synthetase gene is established by Northern hybridisation, since a non-transcribed neighbouring fragment does not hybridise with the corresponding RNA (Example 15). The DNA sequence of the cloned DNA of the cyclosporin synthetase gene is determined and compared with the amino acid partial fragments of cyclosporin synthetase (Examples 13 and 14).

Hence it is possible to transform *Tolypocladium niveum* with the complete gene for cyclosporin synthetase. Among the transformants, strains may be found which contain several copies of this gene or copies with altered regulation. Those strains are selected which, in fermentation tests, display increased cyclosporin formation or can form the same quantity of cyclosporin over a shorter fermentation period.

It is also possible to select the transformed strains by the activity of the cyclosporin synthetase, independently of whether cyclosporin is formed in greater quantities or faster. The isolated cyclosporin synthetase gene can act as an analytical aid in order to determine whether a specific strain of *Tolypocladium niveum* has a high concentration of the mRNA or not (Example 15). Such strains may then be subjected to conventional mutagenesis and strain selection. Even if the initial strain used for transformation is not limited in its cyclosporin synthetase activity, a strain is provided in this way which potentially allows greater cyclosporin formation. The combination of classical genetics (mutation and strain selection) with molecular genetics (transformation with isolated genes) allows the isolation of improved strains which could not be achieved by either of the two methods alone: not by classical genetics because a double mutation is extremely rare in a single selection stage; not by molecular genetics because in some circumstances an unknown factor has a limiting effect.

A further use of the isolated gene is gene-specific mutagenesis. Instead of producing mutations in the entire genome - and therefore also altering many uninvolved genes - the isolated gene alone is mutated using suitable methods (Sambroock *et al.*, 1989) and then transformed to *Tolypocladium niveum* (Example 17). Among the transformants, the proportion of mutants in the cyclosporin synthetase gene is higher than with mutagenesis of the fungus. Mutants, which form specific cyclosporins in greater or reduced quantities, may more frequently be found than with conventional mutagenesis.

By internal sequence comparisons of the derived amino acid sequences (Example 14c) and the correlation of specific partial sequences (Example 8 and Example 9 or Example 14ab), domains of the cyclosporin synthetase for the activation of the individual amino acids may be localised (as performed above for non-ribosomal peptid synthetases). By this means, well-directed mutagen sis of cycl sporin synthetase gen may b performed, by interchanging th gene region f individual domains, by deliberat ly removing a corresp nding regi n or th cyclosporin synthetase gene may also be ext nded by individual domains. After transformation of such mutated genes into *Tolypocladium niveum*, new cyclosporin variants may becom accessibl . The cloned

gene may be used to produce strains of *Tolypocladium niveum* which no longer have an active cyclosporin synthetase gene. Such strains may be used for the production of D-alanine or Bmt by fermentation or act as recipient strains for *in vitro* modified cyclosporin synthetase genes. To this end, an inactive version produced *in vitro* is constructed for the transformation (Example 18).

When screening for microorganisms which can synthesise cyclosporins, it is necessary that the active metabolites under test conditions are also actually formed in sufficient quantity. Such substances may moreover have slightly changed characteristics and may for this reason alone be overlooked. Example 16 describes the use of the isolated cyclosporin synthetase gene to find microorganisms which contain the cyclosporin synthetase gene in their genome. These genes do not have to be active for this purpose. On the basis of these hybridisations, the corresponding genes may be isolated in a manner analogous to Examples 10, 11 and 12 and transformed into *Tolypocladium niveum*. A strain may be used to this end which no longer contains any active cyclosporin synthetase. This interspecific recombination cannot be achieved with other methods. As described in the preceding paragraph, such strains may be subjected to a screening programme. In this case, genetic variability is based on the introduced gene which hybridises with the cyclosporin synthetase gene.

The control sequences of the cyclosporin synthetase gene may also be used for the construction of plasmids. An example of a control sequence is that which occurs in synp4 (Example 12). The promoter may be fused with a readily detectable reporter gene, such as for example the β-glucuronidase gene (Tada *et al.*, 1991). Strains of *Tolypocladium niveum* which are transformed with these plasmids permit, not only the selection of regulatory mutants, but moreover make it possible to measure and optimise promoter activity independently of other functions.

The following examples and figures illustrate the invention without, however, limiting it.

Figure 1: Restriction map of cyclosporin synthetase gene from *Tolypocladium niveum* cloned in λSYN3. The position of some restriction cleavage points is shown in relation to a scale (2.0, 4.0, 6.0, etc. kb). Among these, several partial fragments subcloned in plasmids are represented as rectangles (S5, E3, S3, etc.). If the corresponding rectangle is filled in, this means that the corresponding DNA fragment reacts with a high molecular weight RNA in Northern hybridisation (S5, E3, S3, E1, E2). Rectangles with lengthwise lines indicate that no bands were obtained in Northern hybridisation (E4, S2). Empty rectangles indicate that the DNA was not used as a probe (S4). The following two tables give the positions of the fragments (S5, H2, etc) and enzyme restriction sites shown in figure 1 (in bp):

Start	End	Fragment Name
1	2500	S5
1300	3300	H2
2000	5400	E3
2500	5300	S3
4700	11750	H3
5300	8400	S4
5400	7000	E1
7000	9200	E2
9200	12100	E4
10250	13850	S2

Enzym Restriction sites :					
SalI	1,	HindIII	1300,	EcoRI	2000,
SalI	2500,	HindIII	3300,	HindIII	3800,
HindIII	4700,	SalI	5300,	EcoRI	5400,
EcoRI	7000,	SalI	8400,	EcoRI	9200,
SalI	10250,	HindIII	11750,	EcoRI	12100,
SalI	13850.				

Figure 2: Restriction map of plasmid pSIM10. The construction and structure of the plasmid is described in Example 18. The positions are stated in bp. Nucleotides 4749-6865 are DNA from *Tolypocladium niveum* containing the promoter of the cyclophilin gene. Nucleotides 1-1761 contain the hygromycin phosphotransferase gene from plasmid pCSN44 (Staben *et al.*, 1989). Nucleotides 1761-4714 are from plasmid pGEM7Zf (Promega Inc.).

Figure 3: Restriction map of plasmid pSIM11. Construction of the plasmid is described in Example 18. Nucleotides 4924 to 8553 are the 3.6 kb XhoI restriction fragment from the cyclosporin synthetase gene. Nucleotides 8548-10489 and 1-4929 are plasmid pSIM10 (figure 2).

Figure 4: Restriction map of plasmid pSIM12. Construction of the plasmid is described in Example 18. Nucleotides 4924 to 5727 are the 0.8 kb XhoI restriction fragment from the cyclosporin synthetase gene. Nucleotides 5722-7663 and 1-4929 are plasmid pSIM10 (figure 2).

Figure 5: Restriction map of cyclosporin synthetase gene from *Tolypocladium niveum* cloned in syncosl3. The position of some restriction cleavage points is shown. The position of the part cloned in λsyn3 is marked with the crosshatched bar.

All the restriction maps shown in figures 1, 2, 3, 4 and 5are only approximate reproductions of restriction cleavage points in DNA molecules. The distances as drawn are proportional to the actual distances, but the actual distances may be different. Not all restriction cleavage point are shown, it is possible for further cleavage points to be present.

Example 1: Isolation of active cyclosporin synthetase in electrophoretically homogeneous form:

The starting material used for the protein purification is *Tolypocladium niveum,* strain 7939/45 (Lawen *et al.*, 1989). All steps are performed at a temperature between 0° and 4°C. 10 g of lyophilised mycelium is finely ground in a mortar with addition of liquid nitrogen and then suspended in buffer A (buffer A: 0.2 M HEPES pH 7.8, 0.3 M KCl, 4 mM EDTA, 40 (v/v)% glycerol, 10 mM DTT). The suspension is carefully stirred over ice for 1 hour and then centrifuged for 10 min at 10,000 g to remove cell debris.

The supernatant is collected and nucleic acids are precipitated with polyethyleneimine (final concentration 0.1%). The precipitate is removed by centrifugation for 10 min at 10,000 g.

The supernatant is again collected and proteins are precipitated using a solution of ammonium sulphate (saturated) in buffer B (0.1 M HEPES pH 7.8, 4 mM EDTA, 15 (v/v)% glycerol, 4 mM DTT) at room temperature. The solution is added dropwise to the supernatant up to a final concentration of 50% of saturation. The mixture is left to stand for a further 30 minutes to reach equilibrium. The precipitated proteins are collected by centrifugation for 30 minutes at 30,000 g. The pellet obtained is resolubilised to 10 ml in buffer B.

The resolubilised pellet is then subjected to molecular sieve chromatography. The molecular sieve is a HW65-F Fractogel obtained from Merck; the column dimensions are 2.6 cm x 93 cm, and the volume is 494 ml. The column is operated under fast performance liquid chromatography (FPLC) conditions. The flow rate is 2 ml/min, continuous under buffer B. The cyclosporin synthetase elutes under these conditions at an elution volume of 260 to 310 ml. Processing 10 g of lyophilised mycelium produces 50 mg of cyclosporin synthetase in electrophoretically homogeneous form within 10 hours.

Example 2: Detection of enzymatic activity of cyclosporin synthetase :

80 µl of an nzyme sample in buffer B are incubated, in a t tal volume of 130 µl, with 3.5 mM ATP, 8 mM $MgCl_2$, 10 mM DTT, 10 µM C9 acid, 690 µM of any th r constitu nt amino acid and 100 µM S-ad n syl-methionine + 2 µCi of adenosyl-L-m thionine-S-[methyl-^{3}H] (75 Ci/mmol) for 1 hour at 22°C. Extraction and de-

tection of th cyclosporin A formed are perform d as described in Billich and Z ch r 1987.

Example 3: Endoproteinase cleavages:

The following nd proteinases (Boehringer Mannh im, sequ ncing grade) are used: trypsin from bovin pancreas (cleaves after arginine and lysine); LysC from *Lysobacter enzyrnogenes* (cleaves after lysine); GluC = V8 from *Staphylococcus aureus* (cleaves after glutamic acid and aspartic acid).

The cleavages are not performed under the conditions recommended by the manufacturer; but rather under 'sub-optimal' conditions. The cyclosporin synthetase is incubated in its storage buffer (0.1 M HEPES pH 7.5, 4 mM EDTA, 4 mM DTT, 15 (w/v)% glycerol) with protease in a ratio of 100 µg : 1 µg for 2 to 3 hours at 25°C. In this way, fragments of a size up to approximately 200 kDa are produced.

Example 4: MonoQ purification of fragments:

Purification is performed using a commercially available MonoQ column (HR 5/5) obtained from PHARMACIA, at 4°C. The protease digested protein sample is diluted (1:5) in buffer 1 (20 mM HEPES pH 7.5, 2 mM EDTA, 2 mM DTT, 5 w/v% glycerol) and applied to the column. The gradient elution of fragments is carried out in 20 ml of 0% to 100% buffer 2 (buffer 1 + 500 mM NaCl).

Example 5: HP-RPC purification of MonoQ fractions:

Purification is performed using a commercially available Nucleosil 300A-C4-5µ column of dimensions 85 x 4.5 mm. The MonoQ fraction sample is diluted (1:5) in buffer 1 (5% acetonitrile, 0.1% TFA) and applied at a flow rate of 1 ml/min and room temperature. Gradient elution is carried out in 85 minutes from 0% to 100% buffer 2 (90% acetonitrile, 0.1% TFA).

Example 6: SDS-PAGE/Blot purification of MonoQ fractions:

SDS-PAGE is performed according to Lämmli (1970). Thioglycolic acid (2 mM) is added to the electrophoresis buffer in order to prevent the N termini being blocked by residual radicals from the polymerisation reaction. The MonoQ fractions are used after denaturation with SDS for the electrophoresis. For sequencing, the proteins are blotted out of the gel onto glass fibre membranes ("Glassybond" from Biometra) using the semi-dry method.

Example 7: Protein fragment with methyl transferase activity: identification and purification

The active centre of methyl transferases may be crosslinked with its substrate S-adenosyl-methionine by UV irradiation. This may be exploited by providing a radioactive substrate and so achieving radioactive labelling of the enzyme (Yu *et al.*, 1983). This method, which is also known as "photoaffinity labelling", has been used on cyclosporin synthetase (Lawen and Zocher 1990) and it is possible to show that several labelled protein fragments are produced upon subsequent protease digestion. A labelled fragment is enriched by a combination of the methods described in Examples 4 and 6 and so made accessible to sequencing (see Example 9: aa4). This fragment has a size of approximately 47,000 Dalton.

Example 8: Amino acid activating protein fragments: identification and purification

Protein fragments that have the capacity to activate an amino acid are identified by loading the synthetase with radioactively labelled amino acid in the simultaneous presence of an endoproteinase. Approximately 500 µg of purified cyclosporin synthetase are incubated with 25 mM of ATP, 30 mM $MgCl_2$ and 5 µCi of ^{14}C-L-alanine and are simultaneously treated with, for example, endoproteinase LysC. The reaction is arrested after 3 hours by precipitation of the proteins with TCA. The fragments are resolubilised in a sample buffer for SDS-PAGE, omitting reducing agents. Half of the batch is subjected to SDS-PAGE and the labelled protein fragment is detected by autoradiography of the gel after amplification in "amplify solution" (from NEN) and drying. A fragment with a M_r of approximately 140,000 Dalton is identified and enriched by a combination of the methods described in Examples 4 and 6. The amino acid sequence is giv n in Example 9: aa13.

Exampl 9: Amin acid partial sequences f cyclosporin synth tas :

The following partial sequences ar btained from cyclosporin synth tas obtained from Exampl 6.

aal: amino acids 1916 to 1942 of Seq Id 2 with amin acid 1921 being S and 1942 b ing I
aa2: amino acids 2906 to 2925 of Seq Id 2
aa3: amino acids 12240 to 12261 of Seq Id 2 with amino acid 12254 being E.
aa4: amino acids 6535 to 6550 of Seq Id 2
aa5: amino acids 12654 to 12671 of Seq Id 2
aa6: amino acids 1099 to 1117 of Seq Id 2 with amino acids 1116 and 1117 being V and L
aa8: amino acids 1984 to 1996 of Seq Id 2 with amino acid 1991 undeterminable.
aa9: amino acids 13718 to 13738 of Seq Id 2 with amino acid 13731 undeterminable.
aa10: amino acids 9611 to 9622 of Seq Id 2
aa12: amino acids 11475 to 11484 of Seq Id 2
aa13: amino acids 13601 to 13620 of Seq Id 2
aa14: amino acids 9549 to 9568 of Seq Id 2 with amino acid 9565 undeterminable.
aa15: amino acids 9504 to 9521 of Seq Id 2
aa16: amino acids 13569 to 13586 of Seq Id 2 with amino acid 13568 being G
aa17: amino acids 1020 to 1034 of Seq Id 2
aa19: amino acids 9070 to 9084 of Seq Id 2 with amino acids 9082 and 9083 undeterminable
aa20: amino acids 6532 to 6546 of Seq Id 2 with amino acid 6545 undeterminable

Example 10: Isolation of λ-clones which hybridise with an oligonucleotide specific to cyclosporin synthetase

a) Construction of a genomic λ-gene library from *Tolypocladium niveum.*

DNA is isolated from the mycelium of a culture of *Tolypocladium niveum* grown in medium 1 [50 g/l of maltose, 10 g/l of casein peptone (digested with trypsin, Fluka), 5 g/l of KH_2PO_4 and 2.5 g/l of KCl; the pH value is adjusted to 5.6 with phosphoric acid]. 4 ml of a spore suspension of *Tolypocladium niveum* strain ATCC 34921 with 4 x 10^8 spores per ml are added to 200 ml of medium 1 in a 1 l conical flask and are shaken for 72 hours at 25°C and 250 rpm. The mycelium is filtered off with a Büchner funnel, washed with 10 mM of tris-Cl pH 8.0, 1 mM EDTA and ground to a fine powder under liquid nitrogen. Nuclei are isolated from 40 g of moist mycelial mass and are then lysed; the DNA is purified by CsCl-EtBr centrifugation. This method is described in Jofuku and Goldberg (1988). 4.3 mg of DNA are obtained, which, in a 0.5% agarose gel, produces a band exhibiting lower mobility than λ-DNA.

40 µg of the DNA are incubated with 1.4 units of the restriction enzyme *Sau3A* in 10 mM of tris-Cl pH 7.5, 10 mM $MgCl_2$, 1 mM of DTE, 50 mM of NaCl for 60 minutes at 37°C and then 10 minutes at 65°C. The extent of cleavage is verified on an agarose gel: part of the DNA is between 10 and 20 kb in size. The DNA is then applied to two NaCl gradients, which are produced by freezing and slowly thawing at 4°C two Beckman SW28.1 ultracentrifuge microtubes with 20% NaCl in TE (10 mM tris-Cl, pH 8.0, 1 mM EDTA). The microtubes are centrifuged for 16 hours at 14,000 rpm in Beckman L8M ultracentrifuge in rotor SW28.1. The contents of the microtubes are fractionated. Fractions with DNA larger than 10 kb are combined and dialysed against TE. After concentration of the DNA to 500 µg/ml, the DNA is combined with λEMBL3-DNA (Promega Inc.), previously cleaved with *Eco*RI and *Bam*HI. 1.5 µg of the DNA and 1 µg of λEMBL3-DNA (cleaved with *Eco*RI and *Bam*HI) are ligated for 16 hours at 16°C in 5 µl of 30 mM tris-Cl pH 7.5, 10 mM of $MgCl_2$, 10 mM of DTE, and 2.5 mM ATP after the addition of 0.5 U of T4-DNA ligase (DNA concentration 500 µg/ml). The ligation mixture is packaged *invitro* with the assistance of protein extracts ("packaging mixes", Amersham). The λ-lysates produced are titrated with *E. coli* KW251 (Promega Inc.). Approximately 4.5 x 10^5 pfu are obtained.

b) Isolation of λ-clones

40,000 recombinant phages from the *Tolypocladium niveum* gene library are cast with *E. coli* strain KW251 onto 90 mm TB plates (TB contains 10 g/l of bacto tryptone and 5 g/l of NaCl and 0.7% of agarose, the pH is adjusted to 7.5 with NaOH). Two blots onto nitrocellulose (Stratagene) are made from each plate (Maniatis *et al.*, 1982). From the amino acid sequence of the cyclosporin synthetase fragment aa9 (Example 9), an oligonucleotide mixture (96 different lig nucleotides, ach 20 nucleotides in length) with th sequ nces

5′ GCA TCA ATA TTA AAT TGA TC 3′
G G G G C G
T

may be produced on the basis of the genetic code. 1.5 µg of this oligonucleotide mixture are incubated in 25µl of 50 mM tris-Cl pH 9.5, 10 mM $MgCl_2$, 5 mM DTE, 5% glycerol with 150 µCi γ-ATP (^{32}P) and 20 U of polynucleotide kinase (Boehringer) for 30 minutes at 37°C. Over 80% of the radioactivity is incorporated. Hybridisation is performed at 37°C in 400 ml 6 x SSPE (Maniatis *et al.*, 1982), 5 x Denhardt's solution (Maniatis *et al.*, 1982), 0.1% SDS, 100 µg/ml denatured herring sperm DNA (Maniatis *et al.*, 1982), 0.1 mM ATP, 1.4 x 10^6 cpm/ml ^{32}P-labelled oligonucleotide mixture for 16 hours. The filters are washed three times for 5 minutes and twice for 30 minutes in 6 x SSC (Maniatis *et al.*, 1982) at 4°C. The filters are then washed for 10 minutes at 37°C in a TMAC (tetramethylammonium chloride) washing solution which is prepared according to Wood *et al.*, 1985. Finally, the filters are washed for 30 minutes at 57°C in the TMAC washing solution, dried and exposed for 10 days with a Kodak Xomatik AR X-ray film. Regions of the agarose layer corresponding to positive signals on the X-ray film are punched out and resuspended in SM buffer (5.8 g/l NaCl, 2 g/l $MgSO_4$ x 7 H_2O and 50 mM tris-Cl pH 7.5). A suitable dilution is again cast with KW251 onto a TB plate. The plaques are again transferred onto nitrocellulose. The DNA is isolated from plaques producing a positive hybridisation signal in the second hybridisation. The purified DNA from these phages is used for Southern hybridisations and restriction analyses. Figure 1 shows the restriction map of the *Tolypocladium niveum* proportion of such a λ-clone (= λSYN3). Subcloning is performed in various plasmid vectors (for example pUC18, Pharmacia).

To isolate λ-clones containing the neighbouring DNA fragments ("chromosome walking"), the plaque hybridisation method described above is repeated a number of times; the marginal restriction fragments being used in each case as ^{32}P-labelled probes. In order to clone the DNA adjoining the region shown schematically in figure 1 (λSYN3), fragment S5 is used (figure 1). Hybridisation is then performed at 42°C in 6 x SSPE, 50% formamide, 5 x Denhardt's solution, 0.1% SDS, 100 µg/ml denatured herring sperm DNA, and 100 µM ATP. Before hybridisation, the ^{32}P-labelled DNA is heated to 100°C for 5 minutes and cooled in ice. After 16 to 20 hours, the filters are washed: three times for 10 minutes in 2 x SSC, 0.1% SDS and twice for 30 minutes in 0.2 x SSC, 0.1% SDS at 65°C. The dried filters are autoradiographed. Those areas of the agarose corresponding to positive signals are further processed as described above.

Example 11: Isolation of cosmid clones containing parts of the cyclosporin synthetase gene

a) Construction of a genomic cosmid gene library from *Tolypocladium niveum*

Protoplasts are produced as described in Example 17. Approximately 10^9 protoplasts are carefully lysed in 2 ml of TE (10 mM tris-HCl, 1 mM EDTA, pH 8.0). 0.1 mg/ml of RNase A are added and incubation is continued for 20 minutes at 37°C. After the addition of 0.5% SDS and 0.1 mg/ml of proteinase K, incubation is continued for a further 40 minutes at 55°C. The batch is very carefully extracted twice with each of TE-saturated phenol, phenol/chloroform (1:1) and chloroform/isoamyl alcohol (24:1) (Maniatis *et al.*, 1982). The aqueous, slightly viscous supernatant is combined with one tenth its volume of 3 M sodium acetate (pH 5.2) and covered with a layer of 2.5 times its volume of absolute ethanol at -20°C and the DNA, found as fine threads at the phase interface, wound up using glass rods. The DNA is dissolved in 3 ml of TE for at least 20 hours. Depending on the quality of the protoplasts, approximately 500 µg/ml of DNA are obtained. Analysis with field inversion gel elecrophoresis (FIGE) (0.8% agarose, 0.5 x TBE (Maniatis *et al.*, 1982), 6 V/cm, forwards pulse 0.2 to 3 sec, pulse ratio 3.0, running time 5 hours) gives a size greater than 150 kb. Two batches of 135 µg of DNA are cleaved with 7.5 and 15 units respectively of restriction enzyme NdeII (from Boehringer Mannheim) for 1 hour at 37°C in 1 ml of buffer (tris-acetate 33 mM, magnesium acetate 10 mM, potassium acetate 66 mM, DTT 0.5 mM, pH 7.9). Aliquots of the cleaved DNA are tested with FIGE and give a maximum size for the fragments obtained of approximately 45 and 30 kb respectively.

Using a gradient mixer, linear NaCl density gradients from 30% to 5% in 3 mM EDTA pH 8.0 are produced in ultracentrifuge microtubes and the DNA fragments applied. After centrifugation for 5 hours at 37,000 rpm and 25°C (Beckman L7-65 ultracentrifuge, rotor SW 41), the gradient is harvested in 500 µl fractions. Fractions with DNA greater than 30 kb and less than 50 kb are dialysed three times for tw hours against TE (tris-HCl 10 mM, EDTA 1 mM, pH 8.0), precipitat d with thanol and each dissolved in 50 µl TE.

sCos1 (from Stratag n) is used as th cloning vector. Th vector arms cleaved with BamHI and XbaI are produced and modified as stated by Evans *t al.*, (1989). 1µg of th cleaved vector are ligated with approxi-

mately 500 ng of the DNA fragments in 20 µl of ligation mix (tris-HCl 66 mM, $MgCl_2$ 5 mM, DTE 1 mM, ATP 1 mM, pH 7.5) with 16 units of T4-DNA ligase (from Boehringer) for 16 hours at 12°C. 4 µl portions of th batch are packaged int lambda phage h ads with packaging xtracts (Gigapak, from Stratagen). *E. coli* SRB (from Stratag n) is used as th host strain for the infection and the bact riophag lambda-competent cells are produced following th m thod of Sambroock t *al.*, (1989). After inf ction, th batches are plat d in aliquots onto LB medium (Maniatis *et al.*, 1982) with 75 µg/ml of ampicillin. Recombinant clones are discernible as colonies after 20 hours at 37°C. In total, approximately 50,000 colonies are obtained, which are then suspended in 0.9% NaCl/20% glycerol and stored at -70°C. Analysis of 40 randomly selected clones by isolation and restriction of the cosmids obtained shows that all the clones contain recombinant cosmids; the average insert size is 36 kb.

b) Isolation of cosmid clones

The cosmid gene library is plated at a density of approximately 2500 colonies per 85 mm plate on LB medium with 75 µg/ml of ampicillin (Maniatis *et al.*, 1982). Transfer of each onto two nylon membranes (Duralon UV, Stratagene) is performed as described in Sambroock *et al.*, (1989). The 1.6 kb HindIII fragment from λsyn3 (see figure 1) is labelled with alpha-^{32}P-dATP using "Random Primin g" (from Stratagene) and is used as a hybridisation probe. Prehybridisation is performed for 6 hours, hybridisation for 18 hours at 42°C in 5 x SSC, 40% formamide, 5 x Denhardt's (Maniatis *et al.*, 1982), 0.1% SDS, 25 mM NaH_2PO_4, pH 6.5, and 250 µg/ml of herring sperm DNA. The filters are washed twice for 10 minutes in 2 x SSC/0.1% SDS at room temperature and twice for 40 minutes in 1 x SSC/0.1% SDS at 60°C. The membranes are exposed for 14 hours on X-ray film (Kodak Xomatic AR). Colonies having positive signals are purified, the corresponding cosmid-DNA isolated from the colonies and characterised by various restriction analyses and hybridisations with the labelled λsyn3 probes, and the vector-DNA sCos1. Figure 5 shows the restriction map of the cloned regions of such a cosmid, syncosl3; the *Tolypocladium niveum* DNA contained in it amounts to approximately 35 kb and also includes the region of λsyn3.

Example 12: Isolation of a P1 clone with the complete gene for cyclosporin synthetase

Protoplasts are produced from *Tolypocladium niveum* as described in Example 17 and suspended at a density of 10^9/ml in TPS. 1 ml portions of this suspension are mixed with 1 ml of 1.6% melted agarose (Incert from FMC) held at 40°C and cast into small 1.5 mm thick blocks using a casting stand (BioRad). After solidifying, the blocks are transferred into lysis buffer (0.45 M EDTA pH 8.0, 1% N-lauroyl sarcosin, 1 mg/ml proteinase K) and incubated for 16 hours at 55°C. The blocks are washed for thrice for 2 hours in 0.5 M EDTA pH 8.0 while being slowly rocked and are then stored at 4°C. Before being cleaved, the blocks are cut into small strips, transferred into Eppendorf microtubes and washed for four times for 2 hours and once for 16 hours in TE. The blocks are preincubated in four parallel batches at 4°C, each in 300 µl BamHI buffer (from NEB), supplemented with 100 µg/ml of bovine serum albumin (from NEB) and 80 µM S-adenosylmethionine, for 3 hours on ice. Then, 2 units of BamHI (from NEB) and 16, 20, 24 or 28 units of BamHI methylase (from NEB) are added to each batch and incubation is continued for a further 90 minutes on ice and then for 1 hour at 37°C. The reactions are arrested by the addition of 20 mM of EDTA and 0.5 mg/ml of proteinase K and incubated at 37°C for 30 minutes.

The blocks are applied to a 1% agarose gel (Seaplaque GTG from FMC) and the DNA fragments separated by pulsed field gel electrophoresis ((Chef DR II from BioRad), 0.5 x TBE (Maniatis *et al.*, 1982), switch interval of 8-16 sec, 150 V, 16 h, 12°C).

The region of DNA fragments between 70 and 100 kb is cut out of the gel and the agarose hydrolysed with β-agarase (from NEB). The DNA solution obtained in this manner is very carefully extracted once with tris-saturated phenol and once with chloroform/isoamyl alcohol (24+1) and then concentrated to a final volume of approximately 100 µl by extraction with 1-butanol.

pNS528tet14-Ad10-SacIIB (from DuPont-NEN) is used as the cloning vector. The vector arms are prepared as stated in Pierce *et al.*, (1992). Approximately 250 ng of the cleaved vector are ligated with approximately 500 ng of the DNA fraction for 16 hours at 16°C (performed as in Example 11, total volume 15 µl). After heating the ligation to 70°C for 10 minutes, 4µl aliquots are cleaved with pacase (from DuPont-NEN) and packaged into bacteriophage P1 envelopes by addition of the "head/tail" extract, as described in Pierce and Sternberg (1991). After infection of E. *coli* NS3529, th preparation is plated onto LB medium (Maniatis t *al.*, 1982) with 25 µg/ml kanamycin and 5% saccharose. R combinant clones becom visible aft r incubation of th plates at 37°C f r 20 h.

In total, approximately 2000 colonies are btain d, which are stored as a pool in 0.9% NaCl/20% glycerol

at -70°C as "P1 library".

The gene library (10 x 500 colonies) is screened as described in Example 11 (cosmid clones). *Inter alia*, a positive clone is obtained which contains all the fragments of the cosmid clone syncosl3, together with additionally a further approximately 30 kb of the cyclosporin synthetase gene in the 5' direction. Hybridisation with oligonucleotide mixtures derived from suitable amino acid sequences (see Example 9 and Example 10) shows that all the tested sequences are present on this P1 clone (synp4). In this way, it is ensured that the complete gene for cyclosporin synthetase is contained on this clone synp4.

Example 13: DNA partial sequence of the cyclosporin synthetase gene from *Tolypocladium niveum* ATCC34921

a) The DNA cloned as described in Examples 11 and 12 is sequenced and is illustrated as Seq Id 1.
b) A polypeptide with the amino acid sequence illustrated as Seq Id 2 is be derived from this DNA.

Example 14: Comparison of the amino acid sequences derived from the DNA with the cyclosporin synthetase amino acid partial sequences

The DNA of Seq Id 1 is translated on the basis of the genetic code into an amino acid sequence (*i.e.* position 1 of the protein sequence corresponds to position 885 of the DNA sequence) and is compared with the amino acid sequences given in Example 9:
AA-Partial sequence 3: in Seq Id 2, position 12254 is T. Otherwise all amino acids correspond.
AA-Partial sequence 4: all amino acids correspond.
AA-Partial sequence 5: all amino acids correspond.
AA-Partial sequence 9: in Seq Id 2, position 13730 is W. Otherwise all amino acids correspond. (Position 13 of the AA partial sequence aa9 could not be determined.)
AA-Partial sequence 10: all amino acids correspond.
AA-Partial sequence 12: all amino acids correspond.
AA-Partial sequence 13: all amino acids correspond.
AA-Partial sequence 14: in Seq Id 2, position 9565 is C. Otherwise all amino acids correspond.
AA-Partial sequence 15: all amino acids correspond.
AA-Partial sequence 16: Position 1 of the AA partial sequence aa16 does not correspond to the AA sequence of Seq Id 2. Otherwise all amino acids correspond.
AA-Partial sequence 19: in Seq Id 2, positions 9082 and 9083 are R and Y. Otherwise all amino acids correspond.
AA-Partial sequence 20: in Seq Id 2, position 6545 is W. Otherwise all amino acids correspond.

Further, internal comparison of the amino acids 13804-14063 of Seq Id 2 with amino acids 12304-12563 of Seq Id 2 shows that 178 out of 259 amino acids are identical (68.7%). A further 28 amino acid residues (10.8%) are functionally similar. In total, 11 partial regions similar to each other may be identified in this manner.

Example 15: Isolation of RNA from mycelium of *Tolypocladium niveum* and Northern hybridisation

A 1 l conical flask with 100 ml of medium 4 (Dreyfuss *et al.*, 1976) is inoculated with a spore suspension of *Tolypocladium niveum* ATCC34921 (1 x 10^7 spores/ml) and shaken for 96 hours at 250 rpm and 25°C. II conical flasks with 100 ml of medium 5 (Dreyfuss *et al.*, 1976) are inoculated with 10 ml of this preculture and shaken for 7 days at 25°C and 250 rpm. The cyclosporin A concentration is determined (Dreyfuss *et al.*, 1976) to be 100 µg/ml. 8 g of moist mycelial mass is filtered, washed with TE (10 mM tris-Cl pH 7.5, 1 mM EDTA) and ground to a fine powder in a mortar under liquid nitrogen. RNA is then isolated according to the method described by Cathala *et al.*, (1983). 4 mg of RNA are obtained, which are stored at -70°C. 10 µg of the RNA are separated on a denaturing 1.2% agarose gel containing 0.6 M formaldehyde. The electrophoresis buffer is 0.2 M MOPS, 50 mM sodium acetate, 10 mM EDTA, pH 7.0. The RNA is dissolved in a buffer mixed together from 0.72 ml formamide, 0.16 ml of 10 x concentrated electrophoresis buffer, 0,26 ml formaldehyde, 0.18 ml water and 0.10 ml glycerol. The samples are heated to 100°C for 2 minutes and separated at 115 V, 100 mA over 2 hours. The gel is shaken three times for 20 minutes in 10 x SSC, blotted onto Hybond N-Filter and fixed by UV treatment. Hybridisation is performed at 42°C in 6 x SSPE, 50% formamide, 5 x Denhardt's solution, 0.1% SDS, 100 µg/ml denatured herring sperm DNA, and 100 µM ATP. The ^{32}P-labelled DNA (fragments of the cloned DNAs described in Examples 9 to 12) are heated to 100°C for 5 minutes and cooled in ice before hybridisation. After 16 to 20 hours, the filters are washed: three times for 10 minutes in 2 x SSC, 0.1% SDS and twice for 30 minutes in 0.2 x SSC, 0.1% SDS at 65°C. The dried filters are autoradiographed. If the fragment

used as the probe is a fragment of th cyclosporin synthetas g n , a band may be detected n the X-ray film after 24 to 72 hours of autoradiography at -70°C. Th band exhibits distinctly less mobility than th larg st of the comparison RNA used (9500 b; RNA-ladd r, BRL). Figure 1 summarises the results of such hybridisati ns: in relati n t the restriction map of a λ-clon , th isolation of which is described in Example 10, the positions of individual restricti n fragments are giv n which were used as probes in Northern hybridisati ns. The filled-in rectangles indicate that the bands described above may be detected (E2, E3, E1, S3, S5), while the rectangles with the transverse lines stand for those fragments which do not hybridise with such a band (E4, S2). (Fragment S4 was not used as a probe).

Example 16: Identification of homologous synthetase genes

100 ml of medium 1 (Dreyfuss *et al.*, 1976) are inoculated with 1 x 10^8 fungal spores and shaken for 72 hours at 25°C and 250 rpm. The mycelium is filtered out, washed with TE and lyophilised. 100 mg of lyophilised mycelium are added to 700 µl of lysis buffer (200 mM tris-Cl pH 8.5, 250 mM NaCl, 25 mM EDTA, 0.5% SDS) and 100 mg of aluminium oxide powder (Sigma A2039) in an Eppendorf homogeniser and are homogenised. 500 µl of phenol-chloroform are then added and vigorously mixed in. After 15 minutes centrifugation, the extraction is repeated. A volume of 3M sodium acetate pH 5.2 corresponding to 0.1 time the volume of the supernatant are added to the supernant and then a volume of i-propanol corresponding to 0.6 time the volume of the supernatant is thoroughly mixed in. After 5 minutes of centrifugation, the pellet is washed with 70% ethanol, briefly dried and dissolved in 100 µl of TE with 100 µg/ml of RNase and incubated for 15 minutes at 37°C. The phenol-chloroform extraction and ethanol precipitation are then repeated. The precipitated DNA is collected.

5 µl portions of the DNA are cleaved with *Xho*I, separated on an agarose gel and blotted onto a nylon filter. This filters are hybridised with ^{32}P-labelled λSYN3 DNA as a probe. Hybridisation is performed under standard conditions, as described in Example 10 ("chromosome walking"). The hybridisations may, however, also be performed under less stringent conditions.

The following hybridising bands are obtained with DNA from *Tolypocladium niveum* (all data are estimates due to mobility in the gel): 3.6 kb, 3.4 kb, 3.2 kb, 3.0 kb, 2.3 kb, 1.9 kb and 0.7 kb. DNA from *Fusarium solani* ATCC 46829 also displays bands at 3.6 kb, 3.4 kb, 1.9 kb and 0.7 kb together with a further band at approximately 2.1 kb. DNA from *Neocosmospora vasinfecta* ATCC 24402 also displays the bands at 3.6 kb, 3.4 kb, 1.9 kb and 0.7 kb, together with two further bands at 2.9 kb and 1.8 kb. DNA from *Tolypocladium geodes, Acremonium sp. S42160/F, Paecilomyces sp. S84-21622/F, Verticillium sp. 85-22022/F* (Dreyfuss, 1986) each display several hybridising bands in the range 0.7 kb to 7 kb.

On the basis of the DNA sequence Seq Id 1, the following oligonucleotide pairs are be synthesised:

Nucleotides 35073-35092 of Seq Id 1
Nucleotides 37848-37829 of Seq Id 1 (complementary strand)
or also
Nucleotides 40309-40328 of Seq Id 1
Nucleotides 42018-41999 of Seq Id 1(complementary strand)

If 50 ng of the *Tolypocladium geodes* CBS723.70 DNA is amplified with the first of the two oligonucleotide pairs described above (Sambroock *et al.*, 1989): 30 cycles: 1 min 30 sec 94°C; 2 min 30 sec 50°C; 6 minutes 72°C, a 350 bp DNA is produced. If a part of this DNA is sequenced, the sequence given as Seq Id 3 is obtained. This DNA sequence is 75.1% homologous to the corresponding DNA sequence of Seq Id 1.

Also, if 50 ng of the *Neocosmospora vasinfecta* ATCC 24402 DNA is amplified with the second of the two oligonucleotide pairs described above (Sambroock *et al.*, 1989): 30 cycles: 1 minutes 30 sec 94°C; 2 minutes 30 sec 50°C; 6 minutes 72°C, a 1713 bp DNA is produced. If this DNA is sequenced, the sequence given as Seq Id 4 is obtained. This DNA sequence is 96.3% homologous to the corresponding DNA sequence of Seq Id 1.

Example 17: Protoplastisation and transformation of*Tolypocladium niveum*

a) Method 1:

200 ml of medium 1 (maltose (monohydrate) 50 g/l, casein peptone, digested with trypsin (Fluka 70169) 10 g/l, KH_2PO_4 5 g/l, KCl 2.5 g/l pH 5.6) in a conical flask are inoculated with 10^9 spores of *Tolypocladium niveum* and are incubated at 27°C, 250 rpm f r approximately 70 hours. 200 µl of (0.1%) β-mercaptoethanol ar added and incubation continued for a furth r 16 h urs. The mycelium is harvested by centrifugati n (Beckman J2-21 centrifug , rot r JA14, 8000 rpm, 20°C, 5 minutes), washed in 40 ml of TPS (NaCl 0.6 M, KH_2PO_4/NaH_2PO_4

66 mM pH 6.2) and the pellet volume measured by centrifugation in calibrated microtubes at 2000 g (in Beckman GPR centrifuge, GH3.7 rotor, 3000 rpm, 5 minutes). The mycelium is suspended in TPS (3 ml of TPS are used for each 1 ml of pellet volume) and the same volume of protoplastisation solution is added (Novozym 234 10 mg/ml from Novo Industri, batch PPM-2415), cytohelicase 5 mg/ml (from IBF), Zymolyase 20T 1 mg/ml (from Seikagaku Kogyo, batch no. 120491). The suspension is incubated at 27°C at 80 rpm for approximately 60 minutes. The protoplasts are filtered through a milk filter, centrifuged out (700 g, 10 minutes) and taken up in a total of 4 ml of TPS. Each 1 ml of this suspension is layered on to 4 ml of 35% saccharose solution and is centrifuged at 600 g, 20°C for 20 minutes. The protoplast bands at the phase interface are drawn off, each diluted to 10 ml with TPS, centrifuged out, carefully resuspended in 200 µl portions of TPS and the suspensions are combined. For each 1 ml of pellet volume of starting mycelium (see above), approximately 2 x 10^8 protoplasts are obtained.

The protoplast suspension is centrifuged out (700 g, 10 minutes) and suspended in 1 M sorbitol, 50 mM $CaCl_2$ at a density of 1 x 10^8. 90 µl portions of this suspension are combined with 10 µl of the vector DNA to be transformed, which contains the amdS gene from *Aspergillus nidulans*, for example plasmid p3SR2 (Hynes *et al.*, 1983), (1-10 µg dissolved in tris-HCl 10 mM, EDTA 1 mM, pH 8.0) and 25 µl of PEG 6000-Lsg are added (25% PEG 6000, 50 mM $CaCl_2$, 10 mM tris-HCl, pH 7.5, freshly prepared from the stock solutions: 60% PEG 6000 (from BDH), 250 mM tris-HCl pH 7.5, 250 mM $CaCl_2$). The transformation batch is placed on ice for 20 minutes and then a further 500 µl of the mixed PEG 6000 solution are added and carefully mixed in. After 5 minutes at room temperature, 1 ml of 0.9 M NaCl, 50 mM $CaCl_2$ is added, the entire batch added to 7 ml of melted soft agar TMMAAC+N, held at 45°C, and cast onto preheated TMMAAC+N plates. Medium TMMAAC+N contains 6 g/l glucose, 3 g/l KH_2PO_4, 0.5 g/l KCl, 0.4 g/l $MgSO_4 \times 7\ H_2O$, 0.2 g/l $CaCl_2 \times 2\ H_2O$, 8 mM acrylamide, 2.1 g/l CsCl, 1 ml/l trace element solution, and 0.6 M NaCl. 15 g/l of Agar-Agar (Merck) are used for plates and 7 g/l for soft agar. The trace element solution contains 1 mg/ml of $FeSO_4 \times 7\ H_2O$, 9 mg/ml of $ZnSO_4 \times 7\ H_2O$, 0.4 mg/ml of $CuSO_4 \times 5\ H_2O$, 0.1 mg/ml of $MnSO_4 \times H_2O$, 0.1 mg/ml of H_3BO_3 and 0.1 mg/ml of $Na_2MoO_4 \times H_2O$. Transformants are capable of using acrylamide as a source of nitrogen in the medium and may therefore be identified after approximately 3 weeks at 25°C as colonies against weak background growth.

b) Method 2:

Two portions each of 4.0 ml of the *Tolypocladium niveum* spores (ATCC 34921; 5 x 10^8/ml) are introduced into a 1 l conical flask with 200 ml of medium 1 (50 g/l maltose (monohydrate), 10 g/l casein peptone, digested with trypsin, FLUKA 70169, 5 g/l KH_2PO_4, 2.5 g/l KCl, pH 5.6) and are shaken at 25°C at 250 rpm for 65 hours. The mycelium is filtered out over a sterile sintered porcelain filter with GMX nylon gauze and washed with TE (10 mM tris-Cl pH 7.5, 1 mM EDTA) and resuspended in 40 ml of YG (5 g/l yeast extract, 20 g/l dextrose). Centrifugation is carried out at 900 g and 20°C for 5 minutes. The pellet is resuspended in YG (approximately 1 ml pellet in 5 ml) and 5 ml of protoplastisation solution are added to 5 ml of suspension. The protoplastisation solution is produced from a solution containing 1.1 M KCl and 0.1 M citric acid. The pH is adjusted to 5.8 with KOH. Driselase (Sigma D9515) is added (15 mg/ml; storage at -20°C); the suspension remains in the ice for 15 minutes and the starch carrier is removed by centrifugation for 5 minutes at 2000 rpm. Novozym (4 mg/ml) and bovine serum albumin (Sigma A7096, 20 mg/ml) are added. The solution is filtered through Millipore SLGV025LS and remains in the ice until used. The preparation is shaken at 37°C for 2.5 hours at 250 rpm. The preparation is filtered through a milk filter. The protoplasts are centrifuged out (700 g; 20°C; 5 minutes) and carefully resuspended in STC (1.2 M sorbitol, 50 mM $CaCl_2$, 10 mM tris-HCl pH 7.5). 5 ml of 35% saccharose solution are carefully covered with a layer of the suspension and centrifuged (600 g; 20°C; 20 minutes). The bands are drawn off and diluted to approximately 5 ml with STC. 2 x 10^8 protoplasts are obtained from 200 ml of culture.

50 µl of the protoplast suspension (1 x 10^8/ml) are introduced into a sterile Eppendorf tube and 5 µg of plasmid DNA in TE and 12.5 µl of PEG solution (20% PEG 4000, 50 mM $CaCl_2$, 10 mM tris-HCl pH 7.5) are added. This solution is mixed from separately autoclaved stock solutions: 1 M $CaCl_2$, 1 M tris-HCl pH 7.5, 60% PEG 4000 (Riedel de Häen). Once the mixture has stood for 20 minutes in ice, 0.5 ml of PEG solution are added and carefully mixed in. After 5 minutes at room temperature, 1 ml of 0.9 M NaCl, 50 mM $CaCl_2$ are carefully mixed in. The suspension is added to 10 ml of TM88 sorbitol soft agar (20 g/l malt extract, 4 g/l yeast extract, 10 g/l bacto agar, 218 g/l sorbitol, pH 5.7) (45°C) and cast onto TM88 sorbitol plates (10 ml TM88 sorbitol agar: 20 g/l malt extract, 4 g/l yeast extract, 30 g/l bacto agar, 218 g/l sorbitol, pH 5.7). After 15 to 20 hours at 25°C, 10 ml of TM88 sorbitol agar with 600 µg/ml of hygromycin (45°C) are poured over. Hygromycin resistant transformants may be detected after 7 days at 25°C.

Example 18: Construction of vectors pSIM10, PSIM11 and pSIM12 and transformation with these plasmids

a) Isolation of cyclophilin gen from *Tolypocladium niveum*

As described in Example 10, the *Tolypocladium niveum* gene library is screened with a radioactively labelled DNA probe. Hybridisation is performed at 42°C in 6 x SSPE, 30% formamide, 5 x Denhardt's solution, 0.1% SDS, 100 µg/ml denatured herring sperm DNA, and 100 µM ATP. ^{32}P-labelled DNA (fragments of the DNA of the cyclophilin gene from *Neurospora crassa*, Tropschug *et al.*, 1988) are heated to 100°C for 5 minutes and cooled in ice before hybridisation. After 16 to 20 hours, the filters are washed three times for 10 minutes in 2 x SSC, 0.1% SDS and twice for 30 minutes in 1 x SSC, 0.1% SDS at 45°C. The dried filters are autoradiographed. The purified DNA from λ-phages is subcloned in plasmids and characterised by restriction mapping, Southern hybridisation and DNA sequencing. The cDNA sequence of Seq Id 5 is obtained. The sequence is homologous to the cyclophilin gene of *N. crassa*. The start codon ATG is at positions 12-14 and the stop codon TAA is at positions 552-554.

b) Construction of vector pSIM10 and transformation with this plasmid

On the basis of the Seq Id 5, a first oligonucleotide is synthesised which is largely complementary to Seq Id 5 (positions 2 to 29); however, the ATG region (12 to 14) is altered in such a way that a *Cla*I cleavage point (ATCGAT) is produced. A second oligonucleotide contains a sequence of the plasmid pUC18 and a recognition sequence for *Bam*HI and is given as Seq Id 6.

A plasmid containing a 2.7 kb *Eco*RI-*Hind*III fragment from Example 18a cloned into pUC18 is linearised with *Hind*III. 1 ng of the plasmid DNA is amplified with the oligonucleotides described above (Sambroock *et al.*, 1989): 30 cycles: 1 minutes 30 sec 94°C; 2 minutes 30 sec 50°C; 6 minutes 72°C. A 2.1 kb DNA is produced. After chloroform extraction, this DNA is purified by ultrafiltration (Ultrafree MC 100 000; Millipore) and cleaved in the appropriate buffer with the enzymes *Cla*I and *Bam*HI. 50 ng of this DNA are ligated with 50 ng of *Bam*HI and *Cla*I cleaved DNA of the plasmid pGEM7Zf (Promega). The newly produced plasmid is cleaved with *Cla*I and *Xba*I and ligated with a *Cla*I-*Xba*I restriction fragment 1.76 kb in size from the plasmid pCSN44 (Staben *et al.*, 1989). A restriction map of this plasmid (pSIM10) is reproduced in figure 3.

The 2157 bp *Bam*HI-*Cla*I restriction fragment of the plasmid (4714-6865 in figure 3), which contains the cyclophilin gene promoter, has the DNA sequence of Seq Id 7.

The plasmid pSIM10 may be used for the transformation of *Tolypocladium niveum*, as described in Example 17. DNA from the transformants is cleaved with *Bam*HI and, after electrophoresis, blotted on a nylon membrane. The 1.8 kb *Bgl*II fragment from pSIM10 (figure 3) is used as a radioactive probe. In this way, those of the transformants in which the plasmid pSIM10 has been incorporated once or a plurality of times into the genome may be identified.

The *Xho*I cleavage point in plasmid pSIM10 (4924) allows the construction of plasmids which contain defined parts of the cyclosporin synthetase gene with which a deliberate inactivation of the cyclosporin synthetase gene is possible:

pSIM11 contains a 3.6 kb *Xho*I restriction fragment (42285-45909 of Seq Id 1). If the plasmid linearised with EcoRV is used for the transformation, approximately 30% of transformants obtained no longer form cyclosporin. It is shown with Southern hybridisations with DNA from such transformants that an 8.4 kb *Xba*I fragment is no longer detectable, but instead two new restriction fragments with 10.6 kb and 8.2 kb are detected.

pSIM12 contains a 0.8 kb *Xho*I restriction fragment (39663-40461 of Seq Id 1). If the plasmid linearised with SalI is used for the transformation, approximately 30% of transformants obtained no longer form cyclosporin. It is shown with Southern hybridisations with DNA from such transformants than an 8.4 kb *Xba*I fragment is no longer detectable, but instead two new restriction fragments with 10.4 kb and 5.6 kb are detected.

Example 19: Cotransformation with synp4

pSIM10 (Example 18) is used as transformation vector. Together with this vector, equimolar quantities of synp4 (Example 12) are also used in the same transformation batch. These cotransformations are performed according to the method described in Example 17 and *Tolypocladium niveum* ATCC 34921 is used as the starting strain.

Genomic DNA from hygromycin resistant transformants is isolated according to a rapid method. To this end, mycelium is taken from an area of approximately 1 cm^2 of the corresponding colony and transferred into Eppendorf homogenisers. 1 ml lysis buffer (50 mM EDTA, 0.2% SDS) and 100 mg aluminium oxid (grad A5, from Sigma) are added and the roughly homogenised for approximately 5 minutes. After centrifugation (5 min-

utes, 11,000 rpm) the supernatant is extracted once with each of tris-saturated phenol, phenol/chloroform (1:1) and chloroform/isoamyl alcohol (24:1) and the DNA precipitated with isopropanol using the standard procedure (Sambroock *et al.*, 1989).

The DNA is completely restricted with the restriction enzyme *Sal*I, separated with gel electrophoresis and investigated in Southern hybridisations. The 0.8% agarose gel is transferred by vacuum blotting (Vacublot, from Pharmacia) onto a nylon membrane (Duralon-UV from Stratagene) and fixed with UV.

As probe for the hybridisations, the small *Spe*I restriction fragment from the bacteriophage P1 vector pNS-528tet14-Ad10-SacIIB (from DuPont-NEN) is prepared by gel electrophoresis and Geneclean II Kit (from BIO101) and radioactively labelled with alpha ^{32}P dATP by "random primer" synthesis (from Stratagene).

Prehybridisation is performed for approximately 8 to 16 hours at 42°C in 6 x SSC, 50% formamide, 5 x Denhardt's (Maniatis *et al.*, 1982), 0.1% SDS, 0.25 mg/ml denatured herring sperm DNA, and 25 mM NaH_2PO_4 pH 6.5 in a volume of 10 ml per 100 cm^2 of membrane. After addition of the labelled probe, incubation is continued for a further 16 to 20 hours at 42°C. The blot is washed twice for 10 minutes with 2 x SSC/0.1% SDS at 25°C and twice for 30 minutes with 0.5 x SSC/0.1% SDS at 60°C. After autoradiography for approximately 48 to 96 hours at -70°C with Kodak intensifying film onto X-ray film (Xomatic AR, from Kodak), bands become visible on the X-ray film.

Some of the investigated DNAs display hybridisation signals which are attributable to the integration of synp4. The number of signals, which should correlate with the number of integrated synp4 molecules, varies between 1 and 3.

A transformant strain verified in this manner is investigated for cyclosporin A formation by test fermentation in a shaking flask as described by Dreyfuss *et al.* (1976). Whilst approximately 100 µg/ml of cyclosporin A is formed in parallel tests of the untransformed starting strain *Tolypocladium niveum* ATCC 34921, approximately 150 µg/ml of cyclosporin A is detected in tests with the strain in which additional copies of the cyclosporin synthetase gene are present due to the integration of synp4.

Abbreviations used:

ACV	aminoadipyl-cysteinyl-valine
amdS	acetamidase gene
ATCC	American Type Culture Collection
ATP	adenosine triphosphate
bp	base pairs
CBS	Centraalbureau voor Schimmelcultures
DTE	dithioerythritol
DTT	dithiothreitol
EDTA	ethylenediaminetetraacetic acid
HEPES	N-2-hydroxyethyl-piperazine-N-2-propanesulphonic acid
MOPS	3-morpholinepropanesulphonic acid
PEG	polyethylene glycol
pfu	plaque forming units
SDS	sodium dodecyl sulphate
SDS-PAGE	SDS-polyacrylamide gel electrophoresis
SSC	150 mM NaCl, 15 mM sodium citrate, pH 7.0
SSPE	180 mM NaCl, 10 mM sodium phosphate, 1 mM EDTA, pH 7.7
TE	10 mM tris-Cl pH 7.5, 1 mM EDTA
TFA	trifluoroacetic acid
tris	tris(hydroxymethyl)aminomethane
YAC	yeast artificial chromosome

Moreover, the customary abbreviations for the restriction endonucleases are used (*Sau*3A, *Hind*III, *Eco*RI, *Hind*III, *Cla*I etc.; Maniatis *et al.*, 1982). The nucleotide abbreviations **A, T, C, G** are used for DNA sequences and the amino acid abbreviations (Arg, Asn, Asp, Cys etc.; or R, N, D, C etc.) for polypeptides (Sambroock *et al.*, 1989).

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(iii) NUMBER OF SEQUENCES: 7

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46899 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Tolypocladium niveum
(B) STRAIN: ATCC 34921

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GAATTCAGTA TCGGGCAAAT CTTCATGGTG ATGTGAATCT AGCGAGATGA ATGCAGGAGA 60

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CTTTACTTGA TGCGCGATGT CTGCTTTCCT CTAGAATTC 46899

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15281 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Tolypocladium niveum
(B) STRAIN: ATCC 34921

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Met Gly Ala Ile Gly Gln Asp Met Ala Tyr Asp Arg Leu Ala Asn Pro
1 5 10 15

Ser Arg Ala Ser Ser Ile Ser Ser Asn Arg Tyr Ser Glu Pro Val Glu
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Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe Leu His Gln Leu Lys Leu
35 40 45

Gly Ala Ser Trp Asp Ile Thr Pro Ala Ala Ile Arg Leu Arg Gly His
50 55 60

Leu Asp Ile Asp Ala Leu Asn Ala Ala Ser Arg Ala Leu Thr Gln Arg
65 70 75 80

His Glu Thr Leu Arg Thr Thr Phe Lys Glu Gln Asp Gly Val Gly Val
85 90 95

Gln Val Val His Ala Ser Gly Leu Glu Arg Gly Leu Arg Ile Val Asp
100 105 110

Ala Ser Ser Arg Asp Leu Ala Gln Leu Leu Ala Glu Glu Gln Thr Met
115 120 125

Lys Phe Asp Leu Glu Ser Glu Pro Ala Trp Arg Val Ala Leu Leu Lys
130 135 140

Val Ala Glu Asp His His Ile Leu Ser Ile Val Val His His Ile Ile
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Ser Asp Ser Arg Ser Leu Asp Ile Ile Gln Gln Glu Leu Gly Glu Leu

165 170 175

Tyr Thr Ala Ala Ser Gln Gly Lys Ser Ile Ser Ala Cys Pro Leu Gly
180 185 190

Pro Ile Pro Ile Gln Tyr Arg Asp Leu Thr Thr Trp Gln Asn Gln Asp
195 200 205

Glu Gln Val Ala Glu Gln Glu Arg Gln Leu Gly Tyr Trp Ile Glu Gln
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Leu Asp Asn Asn Thr Pro Ala Glu Leu Leu Thr Glu Leu Pro Arg Pro
225 230 235 240

Ala Ile Pro Ser Gly Glu Thr Gly Lys Ile Ser Phe Gln Ile Asp Gly
245 250 255

Ser Val His Lys Glu Leu Leu Ala Phe Cys Arg Ser Gln Gln Val Thr
260 265 270

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275 280 285

Thr Gly Ala Glu Asp Ala Thr Ile Gly Ala Pro Val Ala Asn Arg Asp
290 295 300

Arg Pro Glu Leu Glu Asn Met Val Ala Pro Leu Ala Thr Leu Gln Cys
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Met Arg Val Val Leu Asp Glu Asp Asp Thr Phe Glu Ser Val Leu Arg
325 330 335

Gln Ile Met Ser Val Met Thr Glu Ala His Ala Asn Arg Asp Val Pro
340 345 350

Phe Glu Arg Ile Val Ser Ala Leu Leu Pro Gly Ser Thr Asp Thr Ser
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Arg His Pro Leu Val Gln Leu Met Phe Ala Leu His Pro Ala Gln Asp
370 375 380

Thr Gly Arg Ala Arg Trp Gly Phe Leu Glu Ala Glu Thr Leu Gln Ser
385 390 395 400

Ala Ala Pro Thr Arg Phe Asp Met Glu Met His Leu Phe Glu Gly Asp
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420 425 430

Glu Ala Ile Arg Ser Val Val Ser Ile Phe Arg Glu Val Leu Arg Arg
435 440 445

Gly Ile Ser Glu Pro Ala Val His Val Lys Thr Met Pro Leu Thr Asp
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Gly Leu Ala Ala Ile Arg Asp Met Gly Leu Leu Asp Ile Gly Thr Thr
465 470 475 480

Asp Tyr Pro Arg Glu Ala Ser Val Val Asp Met Phe Gln Glu Gln Val
485 490 495

Ala Leu Asn Pro Ser Ala Thr Ala Val Ala Asp Ala Ser Ser Arg Leu
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Ser Tyr Ser Glu Leu Asp His Lys Ser Asp Gln Leu Ala Ala Trp Leu
515 520 525

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530 535 540

Pro Ser Cys Glu Thr Met Val Ser Phe Leu Gly Ile Leu Lys Ala His
545 550 555 560

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565 570 575

Ser Ile Leu Ser Ala Val Asp Gly His Lys Leu Val Leu Leu Gly Ser
580 585 590

Asn Val Pro Gln Pro Lys Val Asp Val Pro Asp Val Glu Leu Leu Arg
595 600 605

Ile Ser Asp Ala Leu Asn Gly Ser Gln Val Asn Gly Leu Ala Gly Lys
610 615 620

Gln Ala Thr Ala Lys Pro Ser Ala Thr Asp Leu Ala Tyr Val Ile Phe
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Thr Ser Gly Ser Thr Gly Lys Pro Lys Gly Val Met Ile Glu His Arg
645 650 655

Gly Ile Val Arg Leu Val Lys Gly Thr Asn Ile Ile Ser Pro Ala Gln
660 665 670

Ala Ala Val Pro Thr Ala His Leu Ala Asn Ile Ala Phe Asp Leu Ser
675 680 685

Thr Trp Glu Ile Tyr Thr Pro Ile Leu Asn Gly Gly Thr Leu Val Cys
690 695 700

Ile Glu His Ser Val Thr Leu Asp Ser Lys Ala Leu Glu Ala Val Phe
705 710 715 720

Thr Lys Glu Gly Ile Arg Val Ala Phe Leu Ala Pro Ala Leu Ile Lys
725 730 735

Gln Cys Leu Ala Asp Arg Pro Ala Ile Phe Ala Gly Leu Asp Ser Leu
740 745 750

Tyr Ala Ile Gly Asp Arg Phe Asp Arg Arg Asp Ala Leu His Ala Lys
755 760 765

Ser Leu Val Lys His Gly Val Tyr Asn Ala Tyr Gly Pro Thr Glu Asn
770 775 780

Ser Val Val Ser Thr Ile Tyr Ser Val Ser Glu Ala Ser Pro Phe Val
785 790 795 800

Thr Gly Val Pro Val Gly Arg Ala Ile Ser Asn Ser Gly Ala Tyr Val
805 810 815

Met Asp Gln Asp Gln Gln Leu Val Ser Pro Gly Val Met Gly Glu Leu
820 825 830

Val Val Ser Gly Asp Gly Leu Ala Arg Gly Tyr Thr Asp Ser Ala Leu
835 840 845

Asp Lys Asn Arg Phe Val Val Val Gln Ile Asp Gly Glu Ser Ile Arg
850 855 860

Gly Tyr Arg Thr Gly Asp Arg Ala Arg Tyr Ser Leu Lys Gly Gly Gln
865 870 875 880

Ile Glu Phe Phe Gly Arg Met Asp Gln Gln Val Lys Ile Arg Gly His
885 890 895

Arg Ile Glu Pro Ala Glu Val Glu His Ala Leu Leu Asn Ser Asp Gln
900 905 910

Val Arg Asp Ala Ala Val Val Ile Arg Arg Gln Glu Glu Glu Glu Pro
915 920 925

Ala Met Ile Ala Phe Val Thr Thr Gln Gly Thr Leu Pro Asp His Leu
930 935 940

Val Asn Ile Asn Gly Asn Gly His Val Pro Asp Gly Asn Gly Ser Lys
945 950 955 960

Asn Asp Gln Phe Ala Val His Val Glu Ser Glu Leu Arg Arg Arg Leu
965 970 975

Gln Met Leu Leu Pro Ser Tyr Met Met Pro Ala Arg Ile Val Val Leu
980 985 990

Asp His Leu Pro Leu Asn Pro Asn Gly Lys Val Asp Arg Lys Ala Leu
995 1000 1005

Gly Gln Ser Ala Lys Thr Val Gln Lys Ser Lys Leu Val Ser Gln Arg
1010 1015 1020

Val Ala Pro Arg Asn Glu Ile Glu Ala Val Leu Cys Glu Glu Tyr Arg
1025 1030 1035 1040

Ser Val Leu Gly Val Glu Val Gly Ile Thr Asp Asn Phe Phe Asp Leu
1045 1050 1055

Gly Gly His Ser Leu Thr Ala Met Lys Leu Ala Ala Arg Ile Ser Gln
1060 1065 1070

Arg Leu Asp Ile Gln Ala Ser Val Ala Thr Val Phe Glu Gln Pro Met
1075 1080 1085

Leu Ala Asp Leu Ala Ala Thr Ile Gln Arg Gly Ser Thr Leu Tyr Ser
1090 1095 1100

Val Ile Pro Thr Thr Glu Tyr Thr Gly Pro Val Glu Gln Ser Phe Ala
1105 1110 1115 1120

Gln Gly Arg Leu Trp Phe Leu Glu Gln Leu Asn Thr Gly Ala Ser Trp
1125 1130 1135

Tyr Asn Val Met Leu Thr Val Arg Leu Arg Gly His Leu Asp Val Asp
1140 1145 1150

Ala Leu Gly Thr Ala Leu Leu Ala Leu Glu Lys Arg His Glu Thr Leu
1155 1160 1165

Arg Thr Thr Phe Glu Glu Arg Asp Gly Val Gly Met Gln Val Val His
1170 1175 1180

Ser Ser Leu Met Gly Glu Leu Arg Leu Ile Asp Ile Ser Glu Lys Ser
1185 1190 1195 1200

Gly Thr Ala Ala His Glu Ala Leu Met Lys Glu Gln Ser Thr Arg Phe
1205 1210 1215

Asp Leu Thr Arg Glu Pro Gly Trp Arg Val Ala Leu Leu Lys Leu Ala
1220 1225 1230

Asp His His Ile Phe Ser Ile Val Met His His Ile Val Ser Asp Gly

1235 1240 1245

Trp Ser Leu Asp Leu Leu Arg His Glu Leu Gly Gln Leu Tyr Ser Ala
1250 1255 1260

Ala Leu Arg Gly Gln Asp Pro Leu Ser Arg Leu Glu Pro Leu Pro Ile
1265 1270 1275 1280

Gln Tyr Arg Asp Phe Ala Val Trp Gln Lys Gln Asp Ser Gln Gln Lys
1285 1290 1295

Ala Ala His Gln Arg Gln Leu Glu Tyr Trp Thr Lys Gln Leu Ala Asp
1300 1305 1310

Ser Thr Pro Ala Glu Leu Leu Thr Asp Phe Pro Arg Pro Ser Ile Leu
1315 1320 1325

Ser Gly Lys Ala Gly Lys Val Pro Val Ala Ile Glu Gly Ser Leu Tyr
1330 1335 1340

Asp Thr Leu Gln Val Phe Ser Arg Thr His Gln Val Thr Ser Phe Ala
1345 1350 1355 1360

Val Leu Leu Ala Ala Phe Arg Ala Ala His Phe Arg Leu Thr Gly Ser
1365 1370 1375

Asp Asn Ala Thr Ile Gly Val Pro Ser Ala Asn Arg Asn Arg Pro Glu
1380 1385 1390

Leu Glu Asn Val Ile Gly Phe Phe Val Asn Thr Gln Cys Ile Arg Ile
1395 1400 1405

Thr Ile Asp Glu Asn Asp Asn Phe Glu Ser Leu Val Arg Gln Val Arg
1410 1415 1420

Ser Thr Thr Thr Ala Ala Gln Asp Asn Gln Asp Val Pro Phe Glu Gln
1425 1430 1435 1440

Val Val Ser Ser Leu Met Pro Ser Ser Ser Arg Asp Ala Ser Arg Asn
1445 1450 1455

Pro Leu Val Gln Leu Met Phe Ala Leu His Gly Gln Gln Asp Leu Phe
1460 1465 1470

Lys Ile Gln Leu Glu Gly Thr Glu Glu Glu Val Ile Pro Thr Glu Glu
1475 1480 1485

Val Thr Arg Phe Asp Ile Glu Phe His Leu Tyr Gln Gly Ala Ser Lys
1490 1495 1500

Leu Ser Gly Asp Ile Ile Phe Ala Ala Asp Leu Phe Glu Ala Glu Thr
1505 1510 1515 1520

Ile Arg Gly Val Val Ser Val Phe Gln Glu Val Leu Arg Arg Gly Leu
1525 1530 1535

Gln Gln Pro Gln Thr Pro Ile Met Thr Met Pro Leu Thr Asp Gly Ile
1540 1545 1550

Pro Glu Leu Glu Arg Met Gly Leu Leu His Met Val Lys Thr Asp Tyr
1555 1560 1565

Pro Arg Asn Met Ser Val Val Asp Val Phe Gln Gln Gln Val Arg Leu
1570 1575 1580

Ser Ala Glu Ala Thr Ala Val Ile Asp Ser Ser Ser Arg Met Ser Tyr
1585 1590 1595 1600

Ala Glu Leu Asp Gln Arg Ser Asp Gln Val Ala Ala Trp Leu Arg Gln
1605 1610 1615

Arg Gln Leu Pro Ala Glu Thr Phe Val Ala Val Leu Ala Pro Arg Ser
1620 1625 1630

Cys Glu Ala Val Ile Ala Leu Phe Gly Ile Leu Lys Ala Gly His Ala
1635 1640 1645

Tyr Leu Pro Leu Asp Val Asn Val Pro Ala Ala Arg Leu Arg Ala Ile
1650 1655 1660

Leu Ala Glu Val Lys Gly Glu Lys Leu Val Leu Leu Gly Ala Gly Glu
1665 1670 1675 1680

Pro Ser Pro Glu Gly Gln Ser Pro Glu Val Ser Ile Val Arg Ile Ala
1685 1690 1695

Asp Ala Thr Ser Pro Ala Gly His Ala Ser Leu Arg Asp Gly Lys Ser
1700 1705 1710

Lys Pro Thr Ala Gly Ser Leu Ala Tyr Val Ile Phe Thr Ser Gly Ser
1715 1720 1725

Thr Gly Lys Pro Lys Gly Val Met Ile Glu His Arg Gly Val Leu Arg
1730 1735 1740

Leu Val Lys Gln Thr Asn Ile Leu Ser Ser Leu Pro Pro Ala Gln Thr
1745 1750 1755 1760

Phe Arg Met Ala His Met Ser Asn Leu Ala Phe Asp Ala Ser Ile Trp
1765 1770 1775

Glu Val Phe Thr Ala Leu Leu Asn Gly Gly Ser Leu Val Cys Ile Asp
1780 1785 1790

Arg Phe Thr Ile Leu Asp Ala Gln Ala Leu Glu Ala Leu Phe Leu Arg
1795 1800 1805

Glu His Ile Asn Ile Ala Leu Phe Pro Pro Ala Leu Leu Lys Gln Cys
1810 1815 1820

Leu Thr Asp Ala Ala Ala Thr Ile Lys Ser Leu Asp Leu Leu Tyr Val
1825 1830 1835 1840

Gly Gly Asp Arg Leu Asp Thr Ala Asp Ala Ala Leu Ala Lys Ala Leu
1845 1850 1855

Val Lys Ser Glu Val Tyr Asn Ala Tyr Gly Pro Thr Glu Asn Thr Val
1860 1865 1870

Met Ser Thr Leu Tyr Ser Ile Ala Asp Thr Glu Arg Phe Val Asn Gly
1875 1880 1885

Val Pro Ile Gly Arg Ala Val Ser Asn Ser Gly Val Tyr Val Met Asp
1890 1895 1900

Gln Asn Gln Gln Leu Val Pro Leu Gly Val Met Gly Glu Leu Val Val
1905 1910 1915 1920

Thr Gly Asp Gly Leu Ala Arg Gly Tyr Thr Asn Pro Ala Leu Asp Ser
1925 1930 1935

Asp Arg Phe Val Asp Val Ile Ala Arg Gly Gln Leu Leu Arg Ala Tyr
1940 1945 1950

Arg Thr Gly Asp Arg Ala Arg Tyr Arg Pro Lys Asp Gly Gln Val Glu
1955 1960 1965

Phe Phe Gly Arg Met Asp His Gln Val Lys Val Arg Gly His Arg Ile
1970 1975 1980

Glu Leu Ala Glu Val Glu His Ala Leu Leu Ser Ser Ala Gly Val His
1985 1990 1995 2000

Asp Ala Val Val Val Ser Asn Ser Gln Glu Asp Asn Gln Gly Val Glu
2005 2010 2015

Met Val Ala Phe Ile Thr Ala Gln Asp Asn Glu Thr Leu Gln Glu Ala
2020 2025 2030

Gln Ser Ser Asn Gln Val Gln Glu Trp Glu Ser His Phe Glu Thr Thr
2035 2040 2045

Ala Tyr Ala Asp Ile Thr Ala Ile Asp Gln Asn Thr Leu Gly Arg Asp
2050 2055 2060

Phe Thr Ser Trp Thr Ser Met Tyr Asp Gly Thr Leu Ile Asp Lys Arg
2065 2070 2075 2080

Glu Met Gln Glu Trp Leu Asp Asp Thr Met Arg Thr Phe Leu Asp Gly
2085 2090 2095

Gln Ala Ala Gly His Val Leu Glu Ile Gly Thr Gly Thr Gly Met Val
2100 2105 2110

Leu Phe Asn Leu Gly Gln Ala Gly Leu Lys Ser Tyr Ile Gly Leu Glu
2115 2120 2125

Pro Ser Gln Ser Ala Val Gln Phe Val Asn Lys Ala Ala Gln Thr Phe
2130 2135 2140

Pro Gly Leu Glu Gly Lys Ala Gln Val His Val Gly Thr Ala Met Asp
2145 2150 2155 2160

Thr Gly Arg Leu Ser Ala Leu Ser Pro Asp Leu Ile Val Ile Asn Ser
2165 2170 2175

Val Ala Gln Tyr Phe Pro Ser Arg Glu Tyr Leu Ala Glu Val Val Glu
2180 2185 2190

Ala Leu Val Arg Ile Pro Gly Val Arg Arg Ile Phe Phe Gly Asp Met
2195 2200 2205

Arg Thr Tyr Ala Thr His Lys Asp Phe Leu Val Ala Arg Ala Val His
2210 2215 2220

Thr Asn Gly Ser Lys Val Thr Arg Ser Lys Val Gln Gln Glu Val Ala
2225 2230 2235 2240

Arg Leu Glu Glu Leu Glu Glu Glu Leu Leu Val Asp Pro Ala Phe Phe
2245 2250 2255

Thr Ser Leu Lys Glu Ser Leu Ser Glu Glu Ile Glu His Val Glu Ile
2260 2265 2270

Leu Pro Lys Asn Met Lys Val Asn Asn Glu Leu Ser Ser Tyr Arg Tyr
2275 2280 2285

Gly Ala Val Leu His Ile Arg Asn His Asn Gln Asn Gln Ser Arg Ser
2290 2295 2300

Ile His Lys Ile Asn Ala Glu Ser Trp Ile Asp Ph Ala Ser Ser Gln

2305 2310 2315 2320

Met Asp Arg Gln Gly Leu Ala Arg Leu Leu Lys Glu Asn Lys Asp Ala
2325 2330 2335

Glu Ser Ile Ala Val Phe Asn Ile Pro Tyr Ser Lys Thr Ile Val Glu
2340 2345 2350

Arg His Ile Ala Lys Ser Leu Ala Asp Asp His Asp Gly Asp Asp Thr
2355 2360 2365

His Ser Ser Ile Asp Gly Val Ala Trp Ile Ser Ala Ala Arg Glu Lys
2370 2375 2380

Ala Ser Gln Cys Pro Ser Leu Asp Val His Asp Leu Val Gln Leu Ala
2385 2390 2395 2400

Glu Asp Ala Gly Phe Arg Val Glu Val Ser Trp Ala Arg Gln Arg Ser
2405 2410 2415

Gln Asn Gly Ala Leu Asp Val Phe Phe His His Phe Gln Pro Thr Glu
2420 2425 2430

Asn Glu Ser Arg Ala Leu Val Asp Phe Pro Thr Asp Tyr Lys Gly Gln
2435 2440 2445

Gln Ala Arg Ser Leu Thr Asn Arg Pro Leu Gln Arg Val Glu Ser Arg
2450 2455 2460

Arg Ile Glu Ala Gln Val Arg Glu Gln Leu Gln Val Leu Leu Pro Ala
2465 2470 2475 2480

Tyr Met Ile Pro Ala Arg Ile Val Val Leu Gln Asn Met Pro Leu Asn
2485 2490 2495

Thr Ser Gly Lys Val Asp Arg Lys Glu Leu Thr Leu Arg Ala Lys Val
2500 2505 2510

Thr Ala Ala Arg Thr Pro Ser Ser Glu Leu Val Ala Pro Arg Asp Ser
2515 2520 2525

Ile Glu Ala Ile Ile Cys Lys Glu Phe Lys Asp Val Leu Gly Val Glu
2530 2535 2540

Val Gly Ile Thr Asp Asn Phe Phe Asn Val Gly Gly His Ser Leu Leu
2545 2550 2555 2560

Ala Thr Lys Leu Ala Ala Arg Leu Ser Arg Gln Leu Asn Ala Gln Ile
2565 2570 2575

Ala Val Lys Asp Ile Phe Asp Arg Pro Val Ile Ala Asp Leu Ala Ala
2580 2585 2590

Thr Ile Gln Gln Asp Thr Thr Glu His Asn Pro Ile Leu Pro Thr Ser
2595 2600 2605

Tyr Thr Gly Pro Val Glu Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe
2610 2615 2620

Leu Asp Gln Leu Asn Val Gly Ala Thr Trp Tyr Leu Met Pro Phe Ala
2625 2630 2635 2640

Val Arg Leu Arg Gly Pro Leu Val Val Ser Ala Leu Ala Ala Ala Leu
2645 2650 2655

Leu Ala Leu Glu Glu Arg His Glu Thr Leu Arg Thr Thr Phe Ile Glu
2660 2665 2670

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Gln Glu Gly Ile Gly Met Gln Val Ile His Pro Phe Ala Pro Lys Glu
        2675                2680                2685

Leu Arg Val Ile Asp Val Ser Gly Glu Glu Glu Ser Thr Ile Gln Lys
    2690                2695                2700

Ile Leu Glu Lys Glu Gln Thr Thr Pro Phe Asn Leu Ala Ser Glu Pro
2705                2710                2715                2720

Gly Phe Arg Leu Ala Leu Leu Lys Thr Gly Glu Asp Glu His Ile Leu
                2725                2730                2735

Ser Thr Val Met His His Ala Ile Ser Asp Gly Trp Ser Val Asp Ile
            2740                2745                2750

Phe Gln Gln Glu Ile Gly Gln Phe Tyr Ser Ala Ile Leu Arg Gly His
        2755                2760                2765

Asp Pro Leu Ala Gln Ile Ala Pro Leu Ser Ile Gln Tyr Arg Asp Phe
    2770                2775                2780

Ala Thr Trp Gln Arg Gln Ile Phe Gln Val Ala Glu His Arg Arg Gln
2785                2790                2795                2800

Leu Ala Tyr Trp Thr Lys Gln Leu Ala Asp Asn Lys Pro Ala Glu Leu
                2805                2810                2815

Leu Thr Asp Phe Lys Arg Pro Pro Met Leu Ser Gly Arg Ala Gly Glu
            2820                2825                2830

Ile Pro Val Val Val Asp Gly Leu Ile Tyr Glu Lys Leu Gln Asp Phe
        2835                2840                2845

Cys Arg Ile Arg Gln Val Thr Ala Phe Thr Val Leu Leu Ala Ala Phe
    2850                2855                2860

Arg Ala Ala His Tyr Arg Met Thr Gly Thr Glu Asp Ala Thr Ile Gly
2865                2870                2875                2880

Thr Pro Ile Ala Asn Arg Asn Arg Pro Glu Leu Glu Gly Leu Ile Gly
                2885                2890                2895

Phe Phe Val Asn Thr Gln Cys Met Arg Ile Thr Val Asp Val Glu Asp
            2900                2905                2910

Ser Phe Glu Thr Leu Val His Gln Val Arg Glu Thr Thr Leu Ala Ala
        2915                2920                2925

His Ala Asn Gln Asp Val Pro Phe Glu Gln Ile Val Ser Asn Ile Leu
    2930                2935                2940

Pro Gly Ser Ser Asp Thr Ser Arg Asn Pro Leu Val Gln Leu Met Phe
2945                2950                2955                2960

Ala Leu His Ser Gln Gln Asn Leu Gly Lys Val Arg Leu Glu Gly Ile
                2965                2970                2975

Glu Glu Glu Ile Ile Ser Ile Ala Glu Thr Thr Arg Phe Asp Ile Glu
            2980                2985                2990

Phe His Leu Tyr Gln Glu Ala Glu Arg Leu Asn Gly Ser Ile Val Tyr
        2995                3000                3005

Ala Ala Asp Leu Phe Val Pro Glu Thr Ile Gln Ser Val Ile Thr Ile
    3010                3015                3020
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Phe Gln Gly Ile Leu Gln Lys Gly Leu Gly Glu Pro Asp Met Pro Val
3025                3030                3035                3040

Ala Ser Met Ala Leu Asp Gly Gly Leu Glu Ser Leu Arg Ser Thr Gly
                    3045                3050                3055

Leu Leu His Pro Gln Gln Thr Asp Tyr Pro Cys Asp Ala Ser Val Val
            3060                3065                3070

Gln Ile Phe Lys Gln Gln Val Ala Val Asn Pro Asp Val Ile Ala Val
        3075                3080                3085

Arg Asp Glu Ser Thr Arg Leu Ser Tyr Ala Asp Leu Asp Arg Lys Ser
    3090                3095                3100

Asp Gln Val Ala Cys Trp Leu Ser Arg Arg Gly Ile Ala Pro Glu Thr
3105                3110                3115                3120

Phe Val Ala Ile Leu Ala Pro Arg Ser Cys Glu Thr Ile Val Ala Ile
                    3125                3130                3135

Leu Gly Val Leu Lys Ala Asn Leu Ala Tyr Leu Pro Leu Asp Val Asn
            3140                3145                3150

Val Pro Ala Ser Arg Leu Glu Ala Ile Leu Ser Glu Val Ser Gly Ser
        3155                3160                3165

Met Leu Val Leu Val Gly Ala Glu Thr Pro Ile Pro Glu Gly Met Ala
    3170                3175                3180

Glu Ala Glu Thr Ile Arg Ile Thr Glu Ile Leu Ala Asp Ala Lys Thr
3185                3190                3195                3200

Asp Asp Ile Asn Gly Leu Ala Ala Ser Gln Pro Thr Ala Ala Ser Leu
                    3205                3210                3215

Ala Tyr Val Ile Phe Thr Ser Gly Ser Thr Gly Arg Pro Lys Gly Val
            3220                3225                3230

Met Val Glu His Arg Gly Ile Val Arg Leu Thr Lys Gln Thr Asn Ile
        3235                3240                3245

Thr Ser Lys Leu Pro Glu Ser Phe His Met Ala His Ile Ser Asn Leu
    3250                3255                3260

Ala Phe Asp Ala Ser Val Trp Glu Val Phe Thr Thr Leu Leu Asn Gly
3265                3270                3275                3280

Gly Thr Leu Val Cys Ile Asp Tyr Phe Thr Leu Leu Glu Ser Thr Ala
                    3285                3290                3295

Leu Glu Lys Val Phe Phe Asp Gln Arg Val Asn Val Ala Leu Leu Pro
            3300                3305                3310

Pro Ala Leu Leu Lys Gln Cys Leu Asp Asn Ser Pro Ala Leu Val Lys
        3315                3320                3325

Thr Leu Ser Val Leu Tyr Ile Gly Gly Asp Arg Leu Asp Ala Ser Asp
    3330                3335                3340

Ala Ala Lys Ala Arg Gly Leu Val Gln Thr Gln Ala Phe Asn Ala Tyr
3345                3350                3355                3360

Gly Pro Thr Glu Asn Thr Val Met Ser Thr Ile Tyr Pro Ile Ala Glu
                    3365                3370                3375

Asp Pro Phe Ile Asn Gly Val Pro Ile Gly His Ala Val Ser Asn Ser
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3380 3385 3390

Gly Ala Phe Val Met Asp Gln Asn Gln Gln Ile Thr Pro Pro Gly Ala
3395 3400 3405

Met Gly Glu Leu Ile Val Thr Gly Asp Gly Leu Ala Arg Gly Tyr Thr
3410 3415 3420

Thr Ser Ser Leu Asn Thr Gly Arg Phe Ile Asn Val Asp Ile Asp Gly
3425 3430 3435 3440

Glu Gln Val Arg Ala Tyr Arg Thr Gly Asp Arg Val Arg Tyr Arg Pro
3445 3450 3455

Lys Asp Leu Gln Ile Glu Phe Phe Gly Arg Ile Asp His Gln Val Lys
3460 3465 3470

Ile Arg Gly His Arg Ile Glu Pro Ala Glu Val Glu Tyr Ala Leu Leu
3475 3480 3485

Ser His Asp Leu Val Thr Asp Ala Ala Val Val Thr His Ser Gln Glu
3490 3495 3500

Asn Gln Asp Leu Glu Met Val Gly Phe Val Ala Ala Arg Val Ala Asp
3505 3510 3515 3520

Val Arg Glu Asp Glu Ser Ser Asn Gln Val Gln Glu Trp Gln Thr His
3525 3530 3535

Phe Asp Ser Ile Ala Tyr Ala Asp Ile Thr Thr Ile Asp Gln Gln Ser
3540 3545 3550

Leu Gly Arg Asp Phe Met Ser Trp Thr Ser Met Tyr Asp Gly Ser Leu
3555 3560 3565

Ile Lys Lys Ser Gln Met Gln Glu Trp Leu Asp Asp Thr Met Arg Ser
3570 3575 3580

Leu Leu Asp Ser Gln Pro Pro Gly His Val Leu Glu Val Gly Thr Gly
3585 3590 3595 3600

Thr Gly Met Val Leu Phe Asn Leu Gly Arg Glu Gly Gly Leu Gln Ser
3605 3610 3615

Tyr Val Gly Leu Glu Pro Ser Pro Ser Ala Thr Ala Phe Val Asn Lys
3620 3625 3630

Ala Ala Lys Ser Phe Pro Gly Leu Glu Asp Arg Ile Arg Val Glu Val
3635 3640 3645

Gly Thr Ala Thr Asp Ile Asp Arg Leu Gly Asp Asp Leu His Ala Gly
3650 3655 3660

Leu Val Val Val Asn Ser Val Ala Gln Tyr Phe Pro Ser Gln Asp Tyr
3665 3670 3675 3680

Leu Ala Gln Leu Val Arg Asp Leu Thr Lys Val Pro Gly Val Glu Arg
3685 3690 3695

Ile Phe Phe Gly Asp Met Arg Ser His Ala Ile Asn Arg Asp Phe Leu
3700 3705 3710

Val Ala Arg Ala Val His Ala Leu Gly Asp Lys Ala Thr Lys Ala Glu
3715 3720 3725

Ile Gln Arg Glu Val Val Arg Met Glu Glu Ser Glu Asp Glu Leu Leu
3730 3735 3740

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Val Asp Pro Ala Phe Phe Thr Ser Leu Thr Thr Gln Val Glu Asn Ile
3745                3750                3755                3760

Lys His Val Glu Ile Leu Pro Lys Arg Met Arg Ala Thr Asn Glu Leu
                    3765                3770                3775

Ser Ser Tyr Arg Tyr Ala Ala Val Leu His Val Asn Asp Leu Ala Lys
                3780                3785                3790

Pro Ala His Lys Val Ser Pro Gly Ala Trp Val Asp Phe Ala Ala Thr
        3795                3800                3805

Lys Met Asp Arg Asp Ala Leu Ile Arg Leu Leu Arg Gly Thr Lys Ile
    3810                3815                3820

Ser Asp His Ile Ala Ile Ala Asn Ile Pro Asn Ser Lys Thr Ile Val
3825                3830                3835                3840

Glu Arg Thr Ile Cys Glu Ser Val Tyr Asp Leu Gly Gly Asp Ala Lys
                    3845                3850                3855

Asp Ser Asn Asp Arg Val Ser Trp Leu Ser Ala Ala Arg Ser Asn Ala
                3860                3865                3870

Val Lys Val Ala Ser Leu Ser Ala Ile Asp Leu Val Asp Ile Ala Gln
        3875                3880                3885

Glu Ala Gly Phe Arg Val Glu Ile Ser Cys Ala Arg Gln Trp Ser Gln
    3890                3895                3900

Asn Gly Ala Leu Asp Ala Val Phe His His Leu Gly Pro Ser Pro Gln
3905                3910                3915                3920

Ser Ser His Val Leu Ile Asp Phe Leu Thr Asp His Gln Gly Arg Pro
                    3925                3930                3935

Glu Glu Ala Leu Thr Asn His Pro Leu His Arg Ala Gln Ser Arg Arg
                3940                3945                3950

Val Glu Arg Gln Ile Arg Glu Arg Leu Gln Thr Leu Leu Pro Ala Tyr
        3955                3960                3965

Met Ile Pro Ala Gln Ile Met Val Leu Asp Lys Leu Pro Leu Asn Ala
    3970                3975                3980

Asn Gly Lys Val Asp Arg Lys Gln Leu Thr Gln Arg Ala Gln Thr Val
3985                3990                3995                4000

Pro Lys Ala Lys Gln Val Ser Ala Pro Val Ala Pro Arg Thr Glu Ile
                    4005                4010                4015

Glu Arg Val Leu Cys Gln Glu Phe Ser Asp Val Leu Gly Val Asp Ile
                4020                4025                4030

Gly Ile Met Glu Asn Phe Phe Asp Leu Gly Gly His Ser Leu Met Ala
        4035                4040                4045

Thr Lys Leu Ala Ala Arg Ile Ser Arg Arg Leu Glu Thr His Val Ser
    4050                4055                4060

Val Lys Glu Ile Phe Asp His Pro Arg Val Cys Asp Leu Val Leu Ile
4065                4070                4075                4080

Val Gln Gln Gly Ser Ala Pro His Asp Pro Ile Val Ser Thr Lys Tyr
                    4085                4090                4095
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Thr Gly Pro Val Pro Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe Leu
4100 4105 4110

Asp Gln Leu Asn Phe Gly Ala Thr Trp Tyr Leu Met Pro Leu Ala Val
4115 4120 4125

Arg Leu Arg Gly Ala Met Asn Val His Ala Leu Thr Ala Ala Leu Leu
4130 4135 4140

Ala Leu Glu Arg Arg His Glu Leu Leu Arg Thr Thr Phe Tyr Glu Gln
4145 4150 4155 4160

Asn Gly Val Gly Met Gln Lys Val Asn Pro Val Val Thr Glu Thr Leu
4165 4170 4175

Arg Ile Ile Asp Leu Ser Asn Gly Asp Gly Asp Tyr Leu Pro Thr Leu
4180 4185 4190

Lys Lys Glu Gln Thr Ala Pro Phe His Leu Glu Thr Glu Pro Gly Trp
4195 4200 4205

Arg Val Ala Leu Leu Arg Leu Gly Pro Gly Asp Tyr Ile Leu Ser Val
4210 4215 4220

Val Met His His Ile Ile Ser Asp Gly Trp Ser Val Asp Val Leu Phe
4225 4230 4235 4240

Gln Glu Leu Gly Gln Phe Tyr Ser Thr Ala Val Lys Gly His Asp Pro
4245 4250 4255

Leu Ser Gln Thr Thr Pro Leu Pro Ile His Tyr Arg Asp Phe Ala Leu
4260 4265 4270

Trp Gln Lys Lys Pro Thr Gln Glu Ser Glu His Glu Arg Gln Leu Gln
4275 4280 4285

Tyr Trp Val Glu Gln Leu Val Asp Ser Ala Pro Ala Glu Leu Leu Thr
4290 4295 4300

Asp Leu Pro Arg Pro Ser Ile Leu Ser Gly Gln Ala Gly Glu Met Ser
4305 4310 4315 4320

Val Thr Ile Glu Gly Ala Leu Tyr Lys Asn Leu Glu Glu Phe Cys Arg
4325 4330 4335

Val His Arg Val Thr Ser Phe Val Val Leu Leu Ala Ala Leu Arg Ala
4340 4345 4350

Ala His Tyr Arg Leu Thr Gly Ser Glu Asp Ala Thr Ile Gly Thr Pro
4355 4360 4365

Ile Ala Asn Arg Asn Arg Pro Glu Leu Glu Gln Ile Ile Gly Phe Phe
4370 4375 4380

Val Asn Thr Gln Cys Ile Arg Ile Thr Val Asn Glu Asp Glu Thr Phe
4385 4390 4395 4400

Glu Ser Leu Val Gln Gln Val Arg Ser Thr Ala Thr Ala Ala Phe Ala
4405 4410 4415

His Gln Asp Val Pro Phe Glu Lys Ile Val Ser Thr Leu Leu Pro Gly
4420 4425 4430

Ser Arg Asp Ala Ser Arg Asn Pro Leu Val Gln Leu Met Phe Ala Val
4435 4440 4445

His Ser Gln Lys Asn Leu Gly Glu Leu Lys Leu Glu Asn Ala His Ser

4450 4455 4460

Glu Val Val Pro Thr Glu Ile Thr Thr Arg Phe Asp Leu Glu Phe His
4465 4470 4475 4480

Leu Phe Gln Gln Asp Asp Lys Leu Glu Gly Ser Ile Leu Tyr Ser Thr
4485 4490 4495

Asp Leu Phe Glu Ala Val Ser Val Gln Ser Leu Leu Ser Val Phe Gln
4500 4505 4510

Glu Ile Leu Arg Arg Gly Leu Asn Gly Pro Asp Val Pro Ile Ser Thr
4515 4520 4525

Leu Pro Leu Gln Asp Gly Ile Val Asp Leu Gln Arg Gln Gly Leu Leu
4530 4535 4540

Asp Val Gln Lys Thr Glu Tyr Pro Arg Asp Ser Ser Val Val Asp Val
4545 4550 4555 4560

Phe His Glu Gln Val Ser Ile Asn Pro Asp Ser Ile Ala Leu Ile His
4565 4570 4575

Gly Ser Glu Lys Leu Ser Tyr Ala Gln Leu Asp Arg Glu Ser Asp Arg
4580 4585 4590

Val Ala Arg Trp Leu Arg His Arg Ser Phe Ser Ser Asp Thr Leu Ile
4595 4600 4605

Ala Val Leu Ala Pro Arg Ser Cys Glu Thr Ile Ile Ala Phe Leu Gly
4610 4615 4620

Ile Leu Lys Ala Asn Leu Ala Tyr Leu Pro Leu Asp Val Lys Ala Pro
4625 4630 4635 4640

Ala Ala Arg Ile Asp Ala Ile Val Ser Ser Leu Pro Gly Asn Lys Leu
4645 4650 4655

Ile Leu Leu Gly Ala Asn Val Thr Pro Pro Lys Leu Gln Glu Ala Ala
4660 4665 4670

Ile Asp Phe Val Pro Ile Arg Asp Thr Phe Thr Thr Leu Thr Asp Gly
4675 4680 4685

Thr Leu Gln Asp Gly Pro Thr Ile Glu Arg Pro Ser Ala Gln Ser Leu
4690 4695 4700

Ala Tyr Ala Met Phe Thr Ser Gly Ser Thr Gly Arg Pro Lys Gly Val
4705 4710 4715 4720

Met Val Gln His Arg Asn Ile Val Arg Leu Val Lys Asn Ser Asn Val
4725 4730 4735

Val Ala Lys Gln Pro Ala Ala Ala Arg Ile Ala His Ile Ser Asn Leu
4740 4745 4750

Ala Phe Asp Ala Ser Ser Trp Glu Ile Tyr Ala Pro Leu Leu Asn Gly
4755 4760 4765

Gly Ala Ile Val Cys Ala Asp Tyr Phe Thr Thr Ile Asp Pro Gln Ala
4770 4775 4780

Leu Gln Glu Thr Phe Gln Glu His Glu Ile Arg Gly Ala Met Leu Pro
4785 4790 4795 4800

Pro Ser Leu Leu Lys Gln Cys Leu Val Gln Ala Pro Asp Met Ile Ser
4805 4810 4815

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Arg Leu Asp Ile Leu Phe Ala Ala Gly Asp Arg Phe Ser Ser Val Asp
            4820                4825                4830

Ala Leu Gln Ala Gln Arg Leu Val Gly Ser Gly Val Phe Asn Ala Tyr
        4835                4840                4845

Gly Pro Thr Glu Asn Thr Ile Leu Ser Thr Ile Tyr Asn Val Ala Glu
    4850                4855                4860

Asn Asp Ser Phe Val Asn Gly Val Pro Ile Gly Ser Ala Val Ser Asn
4865                4870                4875                4880

Ser Gly Ala Tyr Ile Met Asp Lys Asn Gln Gln Leu Val Pro Ala Gly
                4885                4890                4895

Val Met Gly Glu Leu Val Val Thr Gly Asp Gly Leu Ala Arg Gly Tyr
            4900                4905                4910

Met Asp Pro Lys Leu Asp Ala Asp Arg Phe Ile Gln Leu Thr Val Asn
        4915                4920                4925

Gly Ser Glu Gln Val Arg Ala Tyr Arg Thr Gly Asp Arg Val Arg Tyr
    4930                4935                4940

Arg Pro Lys Asp Phe Gln Ile Glu Phe Phe Gly Arg Met Asp Gln Gln
4945                4950                4955                4960

Ile Lys Ile Arg Gly His Arg Ile Glu Pro Ala Glu Val Glu Gln Ala
                4965                4970                4975

Phe Leu Asn Asp Gly Phe Val Glu Asp Val Ala Ile Val Ile Arg Thr
            4980                4985                4990

Pro Glu Asn Gln Glu Pro Glu Met Val Ala Phe Val Thr Ala Lys Gly
        4995                5000                5005

Asp Asn Ser Ala Arg Glu Glu Glu Ala Thr Thr Gln Ile Glu Gly Trp
    5010                5015                5020

Glu Ala His Phe Glu Gly Gly Ala Tyr Ala Asn Ile Glu Glu Ile Glu
5025                5030                5035                5040

Ser Glu Ala Leu Gly Tyr Asp Phe Met Gly Trp Thr Ser Met Tyr Asp
                5045                5050                5055

Gly Thr Glu Ile Asp Lys Asp Glu Met Arg Glu Trp Leu Asn Asp Thr
            5060                5065                5070

Met Arg Ser Leu Leu Asp Gly Lys Pro Ala Gly Arg Val Leu Glu Val
        5075                5080                5085

Gly Thr Gly Thr Gly Met Ile Met Phe Asn Leu Gly Arg Ser Gln Gly
    5090                5095                5100

Leu Glu Arg Tyr Ile Gly Leu Glu Pro Ala Pro Ser Ala Ala Glu Phe
5105                5110                5115                5120

Val Asn Asn Ala Ala Lys Ser Phe Pro Gly Leu Ala Gly Arg Ala Glu
                5125                5130                5135

Val His Val Gly Thr Ala Ala Asp Val Gly Thr Leu Gln Gly Leu Thr
            5140                5145                5150

Ser Asp Met Ala Val Ile Asn Ser Val Ala Gln Tyr Phe Pro Thr Pro
        5155                5160                5165
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Glu Tyr Leu Ala Glu Thr Ile Lys Ser Leu Val Gln Val Pro Gly Met
5170 5175 5180

Lys Arg Ile Tyr Leu Gly Asp Met Arg Ser Trp Ala Met Asn Arg Asp
5185 5190 5195 5200

Phe Ala Ala Ala Arg Ala Ala Tyr Ser Leu Ala Asp Asn Ala Ser Lys
5205 5210 5215

Asp Arg Val Arg Gln Lys Met Met Glu Leu Glu Glu Lys Glu Glu Glu
5220 5225 5230

Leu Leu Val Asp Pro Ala Phe Phe Thr Ala Leu Ala Ser Gln Leu Gln
5235 5240 5245

Asp Arg Ile Gln His Val Glu Ile Leu Pro Lys Arg Met Lys Ala Thr
5250 5255 5260

Asn Glu Leu Ser Ser Tyr Arg Tyr Ala Ala Val Leu His Ile Ser Asp
5265 5270 5275 5280

Glu Pro Leu Pro Ile Tyr Lys Ile Asp Pro Glu Ala Trp Ile Asn Phe
5285 5290 5295

Glu Gly Ser Arg Leu Thr Arg Glu Ala Leu Ala Gln Val Leu Lys Glu
5300 5305 5310

Asn Glu Asn Ala Glu Ser Val Ala Ile Ser Asn Ile Pro Tyr Ser Lys
5315 5320 5325

Thr Val Val Glu Arg His Ile Val Arg Ser Leu Asp Gln Glu Asp Ala
5330 5335 5340

Asn Ala Pro Glu Glu Ser Met Asp Gly Ser Asp Trp Ile Ser Ala Val
5345 5350 5355 5360

Arg Thr Arg Ala Gln Gln Cys His Thr Leu Ser Ala Ser Asp Leu Phe
5365 5370 5375

Asp Ile Ala Glu Asp Ala Gly Phe Arg Val Glu Val Ser Trp Ala Arg
5380 5385 5390

Gln His Ser Gln His Gly Ala Leu Asp Ala Val Phe His His Leu Lys
5395 5400 5405

Pro Ala Thr Glu Asp Ser Arg Val Leu Ile Lys Phe Pro Thr Asp His
5410 5415 5420

Gln Gly Arg Pro Leu Lys Ser Leu Thr Asn Gln Pro Leu Leu Pro Ala
5425 5430 5435 5440

Gln Ser Arg Arg Ala Glu Leu Leu Ile Arg Glu Gly Leu Gln Thr Leu
5445 5450 5455

Leu Pro Pro Tyr Met Ile Pro Ser Gln Ile Thr Leu Ile Asp Arg Met
5460 5465 5470

Pro Leu Asn Ala Asn Gly Lys Val Asp Arg Arg Glu Leu Ala Arg Arg
5475 5480 5485

Ala Lys Ile Thr Gln Lys Ser Lys Pro Val Glu Asp Ile Val Pro Pro
5490 5495 5500

Arg Asn Ser Val Glu Ala Thr Val Cys Lys Gly Phe Thr Asp Val Leu
5505 5510 5515 5520

Gly Val Glu Val Gly Ile Thr Asp Asn Phe Phe Asn Leu Gly Gly His

5525 5530 5535

Ser Leu Met Ala Thr Lys Leu Ala Ala Arg Leu Gly Arg Gln Leu Asn
5540 5545 5550

Thr Arg Ile Ser Val Arg Asp Val Phe Asp Gln Pro Val Val Ala Asp
5555 5560 5565

Leu Ala Ala Val Ile Gln Arg Asn Ser Ala Pro His Glu Pro Ile Lys
5570 5575 5580

Pro Ala Asp Tyr Thr Gly Pro Val Pro Gln Ser Phe Ala Gln Gly Arg
5585 5590 5595 5600

Leu Trp Phe Leu Asp Gln Leu Asn Val Gly Ala Thr Trp Tyr Leu Met
5605 5610 5615

Pro Leu Gly Ile Arg Leu His Gly Ser Leu Arg Val Asp Ala Leu Ala
5620 5625 5630

Thr Ala Ile Ser Ala Leu Glu Gln Arg His Glu Pro Leu Arg Thr Thr
5635 5640 5645

Phe His Glu Glu Asp Gly Val Gly Val Gln Val Val Gln Asp His Arg
5650 5655 5660

Pro Lys Asp Leu Arg Ile Ile Asp Leu Ser Thr Gln Pro Lys Asp Ala
5665 5670 5675 5680

Tyr Leu Ala Val Leu Lys His Glu Gln Thr Thr Leu Phe Asp Leu Ala
5685 5690 5695

Thr Glu Pro Gly Trp Arg Val Ala Leu Ile Arg Leu Gly Glu Glu Glu
5700 5705 5710

His Ile Leu Ser Ile Val Met His His Ile Ile Ser Asp Gly Trp Ser
5715 5720 5725

Val Glu Val Leu Phe Asp Glu Met His Arg Phe Tyr Ser Ser Ala Leu
5730 5735 5740

Arg Gln Gln Asp Pro Met Glu Gln Ile Leu Pro Leu Pro Ile Gln Tyr
5745 5750 5755 5760

Arg Asp Phe Ala Ala Trp Gln Lys Thr Glu Glu Gln Val Ala Glu His
5765 5770 5775

Gln Arg Gln Leu Asp Tyr Trp Thr Glu His Leu Ala Asp Ser Thr Pro
5780 5785 5790

Ala Glu Leu Leu Thr Asp Leu Pro Arg Pro Ser Ile Leu Ser Gly Arg
5795 5800 5805

Ala Asn Glu Leu Pro Leu Thr Ile Glu Gly Arg Leu His Asp Lys Leu
5810 5815 5820

Arg Ala Phe Cys Arg Val His Gln Ala Thr Pro Phe Val Ile Leu Leu
5825 5830 5835 5840

Ala Ala Leu Arg Ala Ala His Tyr Arg Leu Thr Gly Ala Glu Asp Ala
5845 5850 5855

Thr Leu Gly Thr Pro Ile Ala Asn Arg Asn Arg Pro Glu Leu Glu Asn
5860 5865 5870

Met Ile Gly Phe Phe Val Asn Thr Gln Cys Met Arg Ile Ala Ile Glu
5875 5880 5885

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Glu Asn Asp Asn Phe Glu Ser Leu Val Arg Arg Val Arg Ser Thr Ala
    5890                5895                5900

Thr Ser Ala Phe Ala Asn Gln Asp Val Pro Phe Glu Ser Ile Val Ser
5905                5910                5915                5920

Ser Leu Leu Pro Gly Ser Arg Asp Ala Ser Arg Asn Pro Leu Val Gln
                5925                5930                5935

Val Ile Leu Ala Val His Ser Gln Gln Asp Leu Gly Lys Leu Thr Leu
            5940                5945                5950

Glu Gly Leu Arg Asp Glu Ala Val Asp Ser Ala Ile Ser Thr Arg Phe
        5955                5960                5965

Asp Val Glu Phe His Leu Phe Glu His Ala Asp Arg Leu Ser Gly Ser
    5970                5975                5980

Val Leu Tyr Ala Lys Glu Leu Phe Lys Leu Arg Thr Ile Glu Ser Val
5985                5990                5995                6000

Val Ser Val Phe Leu Glu Thr Leu Arg Arg Ala Leu Asp Gln Pro Leu
                6005                6010                6015

Thr Pro Leu Ala Val Leu Pro Leu Thr Asp Gly Val Gly Glu Ile Ala
            6020                6025                6030

Ser Lys Gly Leu Leu Asp Val Pro Arg Thr Asp Tyr Pro Arg Asp Ala
        6035                6040                6045

Asn Ile Val Glu Val Phe Gln Gln His Val Arg Ala Thr Pro Asp Ala
    6050                6055                6060

Ile Ala Val Lys Asp Ala Thr Ser Ile Leu Thr Tyr Ala Gln Leu Asp
6065                6070                6075                6080

Gln Gln Ser Asp Arg Leu Ala Ile Trp Leu Ser Arg Arg His Met Met
                6085                6090                6095

Pro Glu Thr Leu Val Gly Val Leu Ala Pro Arg Ser Cys Glu Thr Ile
            6100                6105                6110

Ile Ala Met Phe Gly Ile Met Lys Ala Asn Leu Ala Tyr Leu Pro Leu
        6115                6120                6125

Asp Ile Asn Ser Pro Ala Ala Arg Leu Arg Ser Ile Leu Ser Ala Val
    6130                6135                6140

Asp Gly Asn Lys Leu Val Leu Leu Gly Ser Gly Val Thr Ala Pro Glu
6145                6150                6155                6160

Gln Glu Asn Pro Glu Val Glu Ala Val Gly Ile Gln Glu Ile Leu Ala
                6165                6170                6175

Gly Thr Gly Leu Asp Lys Thr Gln Gly Ser Asn Ala Arg Pro Ser Ala
            6180                6185                6190

Thr Ser Leu Ala Tyr Val Ile Phe Thr Ser Gly Ser Thr Gly Lys Pro
        6195                6200                6205

Lys Gly Val Met Val Glu His Arg Ser Val Thr Arg Leu Ala Lys Pro
    6210                6215                6220

Ser Asn Val Ile Ser Lys Leu Pro Gln Gly Ala Arg Val Ala His Leu
6225                6230                6235                6240
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Ala Asn Ile Ala Phe Asp Ala Ser Ile Trp Glu Ile Ala Thr Thr Leu
6245 6250 6255

Leu Asn Gly Ala Thr Leu Val Cys Leu Asp Tyr His Thr Val Leu Asp
6260 6265 6270

Cys Arg Thr Leu Lys Glu Val Phe Glu Arg Glu Ser Ile Thr Val Val
6275 6280 6285

Thr Leu Met Pro Ala Leu Leu Lys Gln Cys Val Ala Glu Ile Pro Glu
6290 6295 6300

Thr Leu Ala His Leu Asp Leu Leu Tyr Thr Gly Gly Asp Arg Val Gly
6305 6310 6315 6320

Gly His Asp Ala Met Arg Ala Arg Ser Leu Val Lys Ile Gly Met Phe
6325 6330 6335

Ser Gly Tyr Gly Pro Thr Glu Asn Thr Val Ile Ser Thr Ile Tyr Glu
6340 6345 6350

Val Asp Ala Asp Glu Met Phe Val Asn Gly Val Pro Ile Gly Lys Thr
6355 6360 6365

Val Ser Asn Ser Gly Ala Tyr Val Met Asp Arg Asn Gln Gln Leu Val
6370 6375 6380

Pro Ser Gly Val Val Gly Glu Leu Val Val Thr Gly Asp Gly Leu Ala
6385 6390 6395 6400

Arg Gly Tyr Thr Asp Pro Ser Leu Asn Lys Asn Arg Phe Ile Tyr Ile
6405 6410 6415

Thr Val Asn Gly Glu Ser Ile Arg Ala Tyr Arg Thr Gly Asp Arg Val
6420 6425 6430

Arg Tyr Arg Pro His Asp Leu Gln Ile Glu Phe Phe Gly Arg Met Asp
6435 6440 6445

Gln Gln Val Lys Ile Arg Gly His Arg Ile Glu Pro Gly Glu Val Glu
6450 6455 6460

Ser Ala Leu Leu Ser His Asn Ser Val Gln Asp Ala Ala Val Val Ile
6465 6470 6475 6480

Cys Ala Pro Ala Asp Gln Asp Ser Gly Ala Glu Met Val Ala Phe Val
6485 6490 6495

Ala Ala Arg Asn Thr Glu Asp Glu Asp Thr Gln Glu Glu Glu Ala Val
6500 6505 6510

Asp Gln Val Gln Gly Trp Glu Thr His Phe Glu Thr Ala Ala Tyr Ser
6515 6520 6525

Glu Val Lys Asp Ile Arg Gln Ser Glu Val Gly Asn Asp Phe Met Gly
6530 6535 6540

Trp Thr Ser Met Tyr Asp Gly Ser Glu Ile Asp Lys Thr Asp Met His
6545 6550 6555 6560

Glu Trp Leu Asn Asp Thr Met Arg Met Ile Leu Asp Ala Arg Glu Pro
6565 6570 6575

Gly His Val Leu Glu Ile Gly Thr Gly Thr Gly Met Val Met Phe Asn
6580 6585 6590

Leu Ala Lys Cys Pro Gly Leu Gln Gly Tyr Val Gly Phe Glu Pro Ser

6595 6600 6605

Lys Ser Ala Ala Gln Phe Val Asn Asp Ala Ala Gln Ser Phe Pro Ala
6610 6615 6620

Leu Lys Asp Gly Arg Ser Ile Val His Val Gly Thr Ala Thr Asp Ile
6625 6630 6635 6640

Asn Lys Ala Gly Pro Ile Gln Pro Arg Leu Val Val Ile Asn Ser Val
6645 6650 6655

Ala Gln Tyr Phe Pro Thr Pro Glu Tyr Leu Phe Arg Val Val Glu Ala
6660 6665 6670

Leu Val Gln Ile Pro Ser Val Glu Arg Ile Val Phe Gly Asp Met Arg
6675 6680 6685

Thr Asn Ala Ile Asn Arg Asp Phe Val Ala Ser Arg Ala Leu His Thr
6690 6695 6700

Leu Gly Glu Lys Ala Asn Lys Arg Leu Val Arg Gln Met Ile Tyr Glu
6705 6710 6715 6720

Leu Glu Ala Asn Glu Glu Glu Leu Leu Thr Asp Pro Ala Phe Phe Thr
6725 6730 6735

Ser Leu Arg Thr Arg Leu Gly Glu Lys Ile Lys His Val Glu Ile Leu
6740 6745 6750

Pro Lys Thr Met Lys Ala Thr Asn Glu Leu Ser Lys Tyr Arg Tyr Ala
6755 6760 6765

Ala Val Leu His Val Arg Gly Ser Arg Glu Gln Ser Thr Ile His Gln
6770 6775 6780

Val Ser Pro Asn Ala Trp Ile Asp Phe Ala Ala Asp Gly Leu Asp Arg
6785 6790 6795 6800

Gln Thr Leu Ile Asn Leu Leu Lys Glu His Lys Asp Ala Gly Thr Val
6805 6810 6815

Ala Ile Gly Asn Ile Pro Tyr Ser Lys Thr Ile Val Glu Arg Phe Val
6820 6825 6830

Asn Lys Ser Leu Ser Glu Asp Asp Met Glu Glu Gly Gln Asn Ser Leu
6835 6840 6845

Asp Gly Ser Ala Trp Val Ala Ala Val Arg Met Ala Ala Gln Ser Cys
6850 6855 6860

Pro Ser Leu Asp Ala Met Asp Val Lys Glu Ile Ala Gln Glu Ala Gly
6865 6870 6875 6880

Tyr Gln Val Glu Val Ser Trp Ala Arg Gln Trp Ser Gln Asn Gly Ala
6885 6890 6895

Leu Asp Ala Ile Phe His His Phe Glu Pro Pro Lys Glu Gly Ala Arg
6900 6905 6910

Thr Leu Ile Glu Phe Pro Thr Asp Tyr Glu Gly Arg Asn Val Asn Thr
6915 6920 6925

Leu Thr Asn Arg Pro Leu Asn Ser Ile Gln Ser Arg Arg Leu Gly Thr
6930 6935 6940

Gln Ile Arg Glu Lys Leu Gln Thr Leu Leu Pro Pro Tyr Met Ile Pro
6945 6950 6955 6960

Ser Arg Ile Met Val Leu Asp Gln Met Pro Val Asn Asn Asn Gly Lys
6965 6970 6975

Ile Asp Arg Lys Glu Leu Val Arg Arg Ala Ile Val Ala Pro Lys Pro
6980 6985 6990

Arg Ser Ala Ala Thr Arg Val Ala Pro Arg Asn Glu Ile Glu Ala Ile
6995 7000 7005

Leu Arg Asp Glu Phe Glu Asp Val Leu Gly Thr Glu Val Ser Val Leu
7010 7015 7020

Asp Asn Phe Phe Asp Leu Gly Gly His Ser Leu Met Ala Thr Lys Leu
7025 7030 7035 7040

Ala Ala Arg Val Ser Arg Arg Leu Asp Ala His Ile Ser Ile Lys Asp
7045 7050 7055

Val Phe Asp Gln Pro Val Leu Ala Asp Leu Ala Ala Ser Ile Gln Arg
7060 7065 7070

Glu Ser Ala Pro His Glu Pro Ile Pro Gln Arg Pro Tyr Thr Gly Pro
7075 7080 7085

Ala Glu Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe Leu Asp Gln Leu
7090 7095 7100

Asn Leu Gly Ala Thr Trp Tyr Leu Met Pro Leu Ala Ile Arg Ile Arg
7105 7110 7115 7120

Gly Gln Leu Arg Val Ala Ala Leu Ser Ala Ala Leu Phe Ala Leu Glu
7125 7130 7135

Arg Arg His Glu Thr Leu Arg Thr Thr Phe Glu Glu Ser Asp Gly Val
7140 7145 7150

Gly Val Gln Ile Val Gly Glu Ala Arg Asn Ser Asp Leu Arg Val His
7155 7160 7165

Asp Val Ser Thr Gly Asp Asp Gly Glu Tyr Leu Glu Val Leu Arg Arg
7170 7175 7180

Glu Gln Thr Val Pro Phe Asp Leu Ser Ser Glu Pro Gly Trp Arg Val
7185 7190 7195 7200

Cys Leu Val Lys Thr Gly Glu Glu Asp His Val Leu Ser Ile Val Met
7205 7210 7215

His His Ile Ile Tyr Asp Gly Trp Ser Val Asp Ile Leu Arg Gly Glu
7220 7225 7230

Leu Gly Gln Phe Tyr Ser Ala Ala Leu Arg Gly Gln Asp Pro Leu Leu
7235 7240 7245

His Ala Asn Pro Leu Pro Ile Gln Tyr Arg Asp Phe Ala Ala Trp Gln
7250 7255 7260

Arg Glu Ala Lys Gln Val Glu Glu His Gln Arg Gln Leu Gly Tyr Trp
7265 7270 7275 7280

Ser Lys Gln Leu Val Asp Ser Thr Pro Ala Glu Leu Leu Thr Asp Leu
7285 7290 7295

Pro Arg Pro Ser Ile Leu Ser Gly Arg Ala Gly Ser Val Asp Val Thr
7300 7305 7310

Ile Glu Gly Ser Val Tyr Gly Ala Leu Gln Ser Phe Cys Arg Thr Arg
7315 7320 7325

Ser Val Thr Thr Phe Val Val Leu Leu Thr Val Phe Arg Ile Ala His
7330 7335 7340

Phe Arg Leu Thr Ala Val Asp Asp Ala Thr Ile Gly Thr Pro Ile Ala
7345 7350 7355 7360

Asn Arg Asn Arg Pro Glu Leu Glu Thr Leu Val Gly Cys Phe Val Asn
7365 7370 7375

Thr Gln Cys Met Arg Ile Ser Ile Ala Asp Asp Asp Asn Phe Glu Gly
7380 7385 7390

Leu Val Arg Gln Val Arg Asn Val Ala Thr Ala Ala Tyr Ala Asn Gln
7395 7400 7405

Asp Val Pro Phe Glu Arg Ile Val Ser Ala Leu Val Pro Gly Ser Arg
7410 7415 7420

Asn Thr Ser Arg Asn Pro Leu Val Gln Leu Met Phe Ala Val Gln Ser
7425 7430 7435 7440

Val Glu Asp Tyr Asp Gln Val Arg Leu Glu Gly Leu Glu Ser Val Met
7445 7450 7455

Met Pro Gly Glu Ala Ser Thr Arg Phe Asp Met Glu Phe His Leu Val
7460 7465 7470

Pro Gly Asp Gln Lys Leu Thr Gly Ser Val Leu Tyr Ser Ser Asp Leu
7475 7480 7485

Phe Glu Gln Gly Thr Ile Gln Asn Phe Val Asp Ile Phe Gln Glu Cys
7490 7495 7500

Leu Arg Ser Val Leu Asp Gln Pro Leu Thr Pro Ile Ser Val Leu Pro
7505 7510 7515 7520

Phe Ser Asn Ala Ile Ser Asn Leu Glu Ser Leu Asp Leu Leu Glu Met
7525 7530 7535

Pro Thr Ser Asp Tyr Pro Arg Asp Arg Thr Val Val Asp Leu Phe Arg
7540 7545 7550

Glu Gln Ala Ala Ile Cys Pro Asp Ser Ile Ala Val Lys Asp Ser Ser
7555 7560 7565

Ser Gln Leu Thr Tyr Ala Gln Leu Asp Glu Gln Ser Asp Arg Val Ala
7570 7575 7580

Ala Trp Leu His Glu Arg His Met Pro Ala Glu Ser Leu Val Gly Val
7585 7590 7595 7600

Leu Ser Pro Arg Ser Cys Glu Thr Ile Ile Ala Tyr Phe Gly Ile Met
7605 7610 7615

Lys Ala Asn Leu Ala Tyr Leu Pro Leu Asp Val Tyr Ala Pro Asp Ala
7620 7625 7630

Arg Leu Ala Ala Ile Leu Asp Thr Val Glu Gly Glu Arg Leu Leu Leu
7635 7640 7645

Leu Gly Ala Gly Val Pro Gln Pro Gly Ile Gln Ile Pro Arg Leu Ser
7650 7655 7660

Thr Ala Tyr Ile Ala Glu Ala Leu Ser His Ala Thr Thr Val Asp Val

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7665                7670                7675                7680

Thr Ser Ile Pro Gln Pro Ser Ala Thr Ser Leu Ala Tyr Val Ile Phe
                7685                7690                7695

Thr Ser Gly Ser Thr Gly Lys Pro Lys Gly Val Met Ile Glu His Arg
            7700                7705                7710

Gly Ile Val Arg Leu Val Arg Asp Thr Asn Val Asn Val Phe Pro Glu
        7715                7720                7725

Ser Gly Ser Ala Leu Pro Val Ser His Phe Ser Asn Leu Ala Trp Asp
    7730                7735                7740

Ala Ala Thr Trp Glu Ile Tyr Thr Ala Val Leu Asn Gly Gly Thr Val
7745                7750                7755                7760

Val Cys Ile Asp Arg Asp Thr Met Leu Asp Ile Ala Ala Leu Asn Ser
                7765                7770                7775

Thr Phe Arg Lys Glu Asn Val Arg Ala Ala Phe Phe Thr Pro Ala Phe
            7780                7785                7790

Leu Lys Gln Cys Leu Ala Glu Thr Pro Glu Leu Val Ala Asn Leu Glu
        7795                7800                7805

Ile Leu His Thr Ala Gly Asp Arg Leu Asp Pro Gly Asp Ala Asn Leu
    7810                7815                7820

Ala Gly Lys Thr Ala Lys Gly Gly Ile Phe Asn Val Leu Gly His Thr
7825                7830                7835                7840

Glu Asn Thr Ala Tyr Ser Thr Phe Tyr Pro Val Val Gly Glu Glu Thr
                7845                7850                7855

Phe Val Asn Gly Val Pro Val Gly Arg Gly Ile Ser Asn Ser His Ala
            7860                7865                7870

Tyr Ile Ile Asp Arg His Gln Lys Leu Val Pro Ala Gly Val Met Gly
        7875                7880                7885

Glu Leu Ile Leu Thr Gly Asp Gly Val Ala Arg Gly Tyr Thr Asp Ser
    7890                7895                7900

Ala Leu Asn Lys Asp Arg Phe Val Tyr Ile Asp Ile Asn Gly Lys Ser
7905                7910                7915                7920

Thr Trp Ser Tyr Arg Thr Gly Asp Lys Ala Arg Tyr Arg Pro Arg Asp
                7925                7930                7935

Gly Gln Leu Glu Phe Phe Gly Arg Met Asp Gln Met Val Lys Ile Arg
            7940                7945                7950

Gly Val Arg Ile Glu Pro Gly Glu Val Glu Leu Thr Leu Leu Asp His
        7955                7960                7965

Lys Ser Val Leu Ala Ala Thr Val Val Val Arg Arg Pro Pro Asn Gly
    7970                7975                7980

Asp Pro Glu Met Ile Ala Phe Ile Thr Ile Asp Ala Glu Asp Asp Val
7985                7990                7995                8000

Gln Thr His Lys Ala Ile Tyr Lys His Leu Gln Gly Ile Leu Pro Ala
                8005                8010                8015

Tyr Met Ile Pro Ser His Leu Val Ile Leu Asp Gln Met Pro Val Thr
            8020                8025                8030
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Asp Asn Gly Lys Val Asp Arg Lys Asp Leu Ala Leu Arg Ala Gln Thr
8035 8040 8045

Val Gln Lys Arg Arg Ser Thr Ala Ala Arg Val Pro Pro Arg Asp Glu
8050 8055 8060

Val Glu Ala Val Leu Cys Glu Glu Tyr Ser Asn Leu Leu Glu Val Glu
8065 8070 8075 8080

Val Gly Ile Thr Asp Gly Phe Phe Asp Leu Gly Gly His Ser Leu Leu
8085 8090 8095

Ala Thr Lys Leu Ala Ala Arg Leu Ser Arg Gln Leu Asn Thr Arg Val
8100 8105 8110

Ser Val Lys Asp Val Phe Asp Gln Pro Ile Leu Ala Asp Leu Ala Asp
8115 8120 8125

Ile Ile Arg Arg Gly Ser His Arg His Asp Pro Ile Pro Ala Thr Pro
8130 8135 8140

Tyr Thr Gly Pro Val Glu Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe
8145 8150 8155 8160

Leu Glu Gln Leu Asn Leu Gly Ala Ser Trp Tyr Leu Met Pro Phe Ala
8165 8170 8175

Ile Arg Met Arg Gly Pro Leu Gln Thr Lys Ala Leu Ala Val Ala Leu
8180 8185 8190

Asn Ala Leu Val His Arg His Glu Ala Leu Arg Thr Thr Phe Glu Asp
8195 8200 8205

His Asp Gly Val Gly Val Gln Val Ile Gln Pro Lys Ser Ser Gln Asp
8210 8215 8220

Leu Arg Ile Ile Asp Leu Ser Asp Ala Val Asp Asp Thr Ala Tyr Leu
8225 8230 8235 8240

Ala Ala Leu Lys Arg Glu Gln Thr Thr Ala Phe Asp Leu Thr Ser Glu
8245 8250 8255

Pro Gly Trp Arg Val Ser Leu Leu Arg Leu Gly Asp Asp Asp Tyr Ile
8260 8265 8270

Leu Ser Ile Val Met His His Ile Ile Ser Asp Gly Trp Thr Val Asp
8275 8280 8285

Val Leu Arg Gln Glu Leu Gly Gln Phe Tyr Ser Ala Ala Ile Arg Gly
8290 8295 8300

Gln Glu Pro Leu Ser Gln Ala Lys Ser Leu Pro Ile Gln Tyr Arg Asp
8305 8310 8315 8320

Phe Ala Val Trp Gln Arg Gln Glu Asn Gln Ile Lys Glu Gln Ala Lys
8325 8330 8335

Gln Leu Lys Tyr Trp Ser Gln Gln Leu Ala Asp Ser Thr Pro Cys Glu
8340 8345 8350

Phe Leu Thr Asp Leu Pro Arg Pro Ser Ile Leu Ser Gly Glu Ala Asp
8355 8360 8365

Ala Val Pro Met Val Ile Asp Gly Thr Val Tyr Gln Leu Leu Thr Asp
8370 8375 8380

Phe Cys Arg Thr His Gln Val Thr Ser Phe Ser Val Leu Leu Ala Ala
8385 8390 8395 8400

Phe Arg Thr Ala His Tyr Arg Leu Thr Gly Thr Leu Asp Ala Thr Val
8405 8410 8415

Gly Thr Pro Ile Ala Asn Arg Asn Arg Pro Glu Leu Glu Gly Leu Ile
8420 8425 8430

Gly Phe Phe Val Asn Thr Gln Cys Met Arg Met Ala Ile Ser Glu Thr
8435 8440 8445

Glu Thr Phe Glu Ser Leu Val Gln Gln Val Arg Leu Thr Thr Thr Glu
8450 8455 8460

Ala Phe Ala Asn Gln Asp Val Pro Phe Glu Gln Ile Val Ser Thr Leu
8465 8470 8475 8480

Leu Pro Gly Ser Arg Asp Thr Ser Arg Asn Pro Leu Val Gln Val Met
8485 8490 8495

Phe Ala Leu Gln Ser Gln Gln Asp Leu Gly Arg Ile Gln Leu Glu Gly
8500 8505 8510

Met Thr Asp Glu Ala Leu Glu Thr Pro Leu Ser Thr Arg Leu Asp Leu
8515 8520 8525

Glu Val His Leu Phe Gln Glu Val Gly Lys Leu Ser Gly Ser Leu Leu
8530 8535 8540

Tyr Ser Thr Asp Leu Phe Glu Val Glu Thr Ile Arg Gly Ile Val Asp
8545 8550 8555 8560

Val Phe Leu Glu Ile Leu Arg Arg Gly Leu Glu Gln Pro Lys Gln Arg
8565 8570 8575

Leu Met Ala Met Pro Ile Thr Asp Gly Ile Thr Lys Leu Arg Asp Gln
8580 8585 8590

Gly Leu Leu Thr Val Ala Lys Pro Ala Tyr Pro Arg Glu Ser Ser Val
8595 8600 8605

Ile Asp Leu Phe Arg Gln Gln Val Ala Ala Ala Pro Asp Ala Ile Ala
8610 8615 8620

Val Trp Asp Ser Ser Ser Thr Leu Thr Tyr Ala Asp Leu Asp Gly Gln
8625 8630 8635 8640

Ser Asn Lys Leu Ala His Trp Leu Cys Gln Arg Asn Met Ala Pro Glu
8645 8650 8655

Thr Leu Val Ala Val Phe Ala Pro Arg Ser Cys Leu Thr Ile Val Ala
8660 8665 8670

Phe Leu Gly Val Leu Lys Ala Asn Leu Ala Tyr Leu Pro Leu Asp Val
8675 8680 8685

Asn Ala Pro Ala Ala Arg Ile Glu Ala Ile Leu Ser Ala Val Pro Gly
8690 8695 8700

His Lys Leu Val Leu Val Gln Ala His Gly Pro Glu Leu Gly Leu Thr
8705 8710 8715 8720

Met Ala Asp Thr Glu Leu Val Gln Ile Asp Glu Ala Leu Ala Ser Ser
8725 8730 8735

Ser Ser Gly Asp His Glu Gln Ile His Ala Ser Gly Pro Thr Ala Thr

8740 8745 8750

Ser Leu Ala Tyr Val Met Phe Thr Ser Gly Ser Thr Gly Lys Pro Lys
8755 8760 8765

Gly Val Met Ile Asp His Arg Ser Ile Ile Arg Leu Val Lys Asn Ser
8770 8775 8780

Asp Val Val Ala Thr Leu Pro Thr Pro Val Arg Met Ala Asn Val Ser
8785 8790 8795 8800

Asn Leu Ala Phe Asp Ile Ser Val Gln Glu Ile Tyr Thr Ala Leu Leu
8805 8810 8815

Asn Gly Gly Thr Leu Val Cys Leu Asp Tyr Leu Thr Leu Leu Asp Ser
8820 8825 8830

Lys Ile Leu Tyr Asn Val Phe Val Glu Ala Gln Val Asn Ala Ala Met
8835 8840 8845

Phe Thr Pro Val Leu Leu Lys Gln Cys Leu Gly Asn Met Pro Ala Ile
8850 8855 8860

Ile Ser Arg Leu Ser Val Leu Phe Asn Val Gly Asp Arg Leu Asp Ala
8865 8870 8875 8880

His Asp Ala Val Ala Ala Ser Gly Leu Ile Gln Asp Ala Val Tyr Asn
8885 8890 8895

Ala Tyr Gly Pro Thr Glu Asn Gly Met Gln Ser Thr Met Tyr Lys Val
8900 8905 8910

Asp Val Asn Glu Pro Phe Val Asn Gly Val Pro Ile Gly Arg Ser Ile
8915 8920 8925

Thr Asn Ser Gly Ala Tyr Val Met Asp Gly Asn Gln Gln Leu Val Ser
8930 8935 8940

Pro Gly Val Met Gly Glu Ile Val Val Thr Gly Asp Gly Leu Ala Arg
8945 8950 8955 8960

Gly Tyr Thr Asp Ser Ala Leu Asp Glu Asp Arg Phe Val His Val Thr
8965 8970 8975

Ile Asp Gly Glu Glu Asn Ile Lys Ala Tyr Arg Thr Gly Asp Arg Val
8980 8985 8990

Arg Tyr Arg Pro Lys Asp Phe Glu Ile Glu Phe Phe Gly Arg Met Asp
8995 9000 9005

Gln Gln Val Lys Ile Arg Gly His Arg Ile Glu Pro Ala Glu Val Glu
9010 9015 9020

His Ala Leu Leu Gly His Asp Leu Val His Asp Ala Ala Val Val Leu
9025 9030 9035 9040

Arg Lys Pro Ala Asn Gln Glu Pro Glu Met Ile Ala Phe Ile Thr Ser
9045 9050 9055

Gln Glu Asp Glu Thr Ile Glu Gln His Glu Ser Asn Lys Gln Val Gln
9060 9065 9070

Gly Trp Gly Glu His Phe Asp Val Ser Arg Tyr Ala Asp Ile Lys Asp
9075 9080 9085

Leu Asp Thr Ser Thr Phe Gly His Asp Phe Leu Gly Trp Thr Ser Met
9090 9095 9100

Tyr Asp Gly Val Asp Ile Pro Val Asn Glu Met Lys Glu Trp Leu Asp
9105 9110 9115 9120

Glu Thr Thr Ala Ser Leu Leu Asp Asn Arg Pro Pro Gly His Ile Leu
9125 9130 9135

Glu Ile Gly Ala Gly Thr Gly Met Ile Leu Ser Asn Leu Gly Lys Val
9140 9145 9150

Asp Gly Leu Gln Lys Tyr Val Gly Leu Asp Pro Ala Pro Ser Ala Ala
9155 9160 9165

Ile Phe Val Asn Glu Ala Val Lys Ser Leu Pro Ser Leu Ala Gly Lys
9170 9175 9180

Ala Arg Val Leu Val Gly Thr Ala Leu Asp Ile Gly Ser Leu Asp Lys
9185 9190 9195 9200

Asn Glu Ile Gln Pro Glu Leu Val Val Ile Asn Ser Val Ala Gln Tyr
9205 9210 9215

Phe Pro Thr Ser Glu Tyr Leu Ile Lys Val Val Lys Ala Val Val Glu
9220 9225 9230

Val Pro Ser Val Lys Arg Val Phe Phe Gly Asp Ile Arg Ser Gln Ala
9235 9240 9245

Leu Asn Arg Asp Phe Leu Ala Ala Arg Ala Val Arg Ala Leu Gly Asp
9250 9255 9260

Asn Ala Ser Lys Glu Gln Ile Arg Glu Lys Ile Ala Glu Leu Glu Glu
9265 9270 9275 9280

Ser Glu Glu Glu Leu Leu Val Asp Pro Ala Phe Phe Val Ser Leu Arg
9285 9290 9295

Ser Gln Leu Pro Asn Ile Lys His Val Glu Val Leu Pro Lys Leu Met
9300 9305 9310

Lys Ala Thr Asn Glu Leu Ser Ser Tyr Arg Tyr Ala Ala Val Leu His
9315 9320 9325

Ile Ser His Asn Glu Glu Glu Gln Leu Leu Ile Gln Asp Ile Asp Pro
9330 9335 9340

Thr Ala Trp Val Asp Phe Ala Ala Thr Gln Lys Asp Ser Gln Gly Leu
9345 9350 9355 9360

Arg Asn Leu Leu Gln Gln Gly Arg Asp Asp Val Met Ile Ala Val Gly
9365 9370 9375

Asn Ile Pro Tyr Ser Lys Thr Ile Val Glu Arg His Ile Met Asn Ser
9380 9385 9390

Leu Asp Gln Asp His Val Asn Ser Leu Asp Gly Thr Ser Trp Ile Ser
9395 9400 9405

Asp Ala Arg Ser Ala Ala Ala Ile Cys Thr Ser Phe Asp Ala Pro Ala
9410 9415 9420

Leu Thr Gln Leu Ala Lys Glu Glu Gly Phe Arg Val Glu Leu Ser Trp
9425 9430 9435 9440

Ala Arg Gln Arg Ser Gln Asn Gly Ala Leu Asp Ala Val Phe His Arg
9445 9450 9455

Leu Ala Thr Asp Ala Asn Cys Glu Arg Ser Arg Val Leu Val His Phe
9460 9465 9470

Pro Thr Asp His Gln Gly Arg Gln Leu Arg Thr Leu Thr Asn Arg Pro
9475 9480 9485

Leu Gln Arg Ala Gln Ser Arg Arg Ile Glu Ser Gln Val Phe Glu Ala
9490 9495 9500

Leu Gln Thr Ala Leu Pro Ala Tyr Met Ile Pro Ser Arg Ile Ile Val
9505 9510 9515 9520

Leu Pro Gln Met Pro Thr Asn Ala Asn Gly Lys Val Asp Arg Lys Gln
9525 9530 9535

Leu Ala Arg Arg Ala Gln Val Val Ala Lys Arg Lys Ala Val Ser Ala
9540 9545 9550

Arg Val Ala Pro Arg Asn Asp Thr Glu Ile Val Leu Cys Glu Glu Tyr
9555 9560 9565

Ala Asp Ile Leu Gly Thr Glu Val Gly Ile Thr Asp Asn Phe Phe Asp
9570 9575 9580

Met Gly Gly His Ser Leu Met Ala Thr Lys Leu Ala Ala Arg Leu Ser
9585 9590 9595 9600

Arg Arg Leu Asp Thr Arg Val Thr Val Lys Glu Val Phe Asp Lys Pro
9605 9610 9615

Val Leu Ala Asp Leu Ala Ala Ser Ile Glu Gln Gly Ser Thr Pro His
9620 9625 9630

Leu Pro Ile Ala Ser Ser Val Tyr Ser Gly Pro Val Glu Gln Ser Tyr
9635 9640 9645

Ala Gln Gly Arg Leu Trp Phe Leu Asp Gln Phe Asn Leu Asn Ala Thr
9650 9655 9660

Trp Tyr His Met Ser Leu Ala Met Arg Leu Leu Gly Pro Leu Asn Met
9665 9670 9675 9680

Asp Ala Leu Asp Val Ala Leu Arg Ala Leu Glu Gln Arg His Glu Thr
9685 9690 9695

Leu Arg Thr Thr Phe Glu Ala Gln Lys Asp Ile Gly Val Gln Val Val
9700 9705 9710

His Glu Ala Gly Met Lys Arg Leu Lys Val Leu Asp Leu Ser Asp Lys
9715 9720 9725

Asn Glu Lys Glu His Met Ala Val Leu Glu Asn Glu Gln Met Arg Pro
9730 9735 9740

Phe Thr Leu Ala Ser Glu Pro Gly Trp Lys Gly His Leu Ala Arg Leu
9745 9750 9755 9760

Gly Pro Thr Glu Tyr Ile Leu Ser Leu Val Met His His Met Phe Ser
9765 9770 9775

Asp Gly Trp Ser Val Asp Ile Leu Arg Gln Glu Leu Gly Gln Phe Tyr
9780 9785 9790

Ser Ala Ala Leu Arg Gly Arg Asp Pro Leu Ser Gln Val Lys Pro Leu
9795 9800 9805

Pro Ile Gln Tyr Arg Asp Phe Ala Ala Trp Gln Lys Glu Ala Ala Gln

9810 9815 9820

Val Ala Glu His Glu Arg Gln Leu Ala Tyr Trp Glu Asn Gln Leu Ala
9825 9830 9835 9840

Asp Ser Thr Pro Gly Glu Leu Leu Thr Asp Phe Pro Arg Pro Gln Phe
9845 9850 9855

Leu Ser Gly Lys Ala Gly Val Ile Pro Val Thr Ile Glu Gly Pro Val
9860 9865 9870

Tyr Glu Lys Leu Leu Lys Phe Ser Lys Glu Arg Gln Val Thr Leu Phe
9875 9880 9885

Ser Val Leu Leu Thr Ala Phe Arg Ala Thr His Phe Arg Leu Thr Gly
9890 9895 9900

Ala Glu Asp Ala Thr Ile Gly Thr Pro Ile Ala Asn Arg Asn Arg Pro
9905 9910 9915 9920

Glu Leu Glu His Ile Ile Gly Phe Phe Val Asn Thr Gln Cys Met Arg
9925 9930 9935

Leu Leu Leu Asp Thr Gly Ser Thr Phe Glu Ser Leu Val Gln His Val
9940 9945 9950

Arg Ser Val Ala Thr Asp Ala Tyr Ser Asn Gln Asp Ile Pro Phe Glu
9955 9960 9965

Arg Ile Val Ser Ala Leu Leu Pro Gly Ser Arg Asp Ala Ser Arg Ser
9970 9975 9980

Pro Leu Ile Gln Leu Met Phe Ala Leu His Ser Gln Pro Asp Leu Gly
9985 9990 9995 10000

Asn Ile Thr Leu Glu Gly Leu Glu His Glu Arg Leu Pro Thr Ser Val
10005 10010 10015

Ala Thr Arg Phe Asp Met Glu Phe His Leu Phe Gln Glu Pro Asn Lys
10020 10025 10030

Leu Ser Gly Ser Ile Leu Phe Ala Asp Glu Leu Phe Gln Pro Glu Thr
10035 10040 10045

Ile Asn Ser Val Val Thr Val Phe Gln Glu Ile Leu Arg Arg Gly Leu
10050 10055 10060

Asp Gln Pro Gln Val Ser Ile Ser Thr Met Pro Leu Thr Asp Gly Leu
10065 10070 10075 10080

Ile Asp Leu Glu Lys Leu Gly Leu Leu Glu Ile Glu Ser Ser Asn Phe
10085 10090 10095

Pro Arg Asp Tyr Ser Val Val Asp Val Phe Arg Gln Gln Val Ala Ala
10100 10105 10110

Asn Pro Asn Ala Pro Ala Val Val Asp Ser Glu Thr Ser Met Ser Tyr
10115 10120 10125

Thr Ser Leu Asp Gln Lys Ser Glu Gln Ile Ala Ala Trp Leu His Ala
10130 10135 10140

Gln Gly Leu Arg Pro Glu Ser Leu Ile Cys Val Met Ala Pro Arg Ser
10145 10150 10155 10160

Phe Glu Thr Ile Val Ser Leu Phe Gly Ile Leu Lys Ala Gly Tyr Ala
10165 10170 10175

Tyr Leu Pro Leu Asp Val Asn Ser Pro Ala Ala Arg Ile Gln Pro Ile
10180 10185 10190

Leu Ser Glu Val Glu Gly Lys Arg Leu Val Leu Leu Gly Ser Gly Ile
10195 10200 10205

Asp Met Pro Gln Ser Asp Arg Met Asp Val Glu Thr Ala Arg Ile Gln
10210 10215 10220

Asp Ile Leu Thr Asn Thr Lys Val Glu Arg Ser Asp Pro Met Ser Arg
10225 10230 10235 10240

Pro Ser Ala Thr Ser Leu Ala Tyr Val Ile Phe Thr Ser Gly Ser Thr
10245 10250 10255

Gly Arg Pro Lys Gly Val Met Ile Glu His Arg Asn Ile Leu Arg Leu
10260 10265 10270

Val Lys Gln Ser Asn Val Thr Ser Gln Leu Pro Gln Asp Leu Arg Met
10275 10280 10285

Ala His Ile Ser Asn Leu Ala Phe Asp Ala Ser Ile Trp Glu Ile Phe
10290 10295 10300

Thr Ala Ile Leu Asn Gly Gly Ala Leu Ile Cys Ile Asp Tyr Phe Thr
10305 10310 10315 10320

Leu Leu Asp Ser Gln Ala Leu Arg Thr Thr Phe Glu Lys Ala Arg Val
10325 10330 10335

Asn Ala Thr Leu Phe Ala Pro Ala Leu Leu Lys Glu Cys Leu Asn His
10340 10345 10350

Ala Pro Thr Leu Phe Glu Asp Leu Lys Val Leu Tyr Ile Gly Gly Asp
10355 10360 10365

Arg Leu Asp Ala Thr Asp Ala Ala Lys Ile Gln Ala Leu Val Lys Gly
10370 10375 10380

Thr Val Tyr Asn Ala Tyr Gly Pro Thr Glu Asn Thr Val Met Ser Thr
10385 10390 10395 10400

Ile Tyr Arg Leu Thr Asp Gly Glu Ser Tyr Ala Asn Gly Val Pro Ile
10405 10410 10415

Gly Asn Ala Val Ser Ser Ser Gly Ala Tyr Ile Met Asp Gln Lys Gln
10420 10425 10430

Arg Leu Val Pro Pro Gly Val Met Gly Glu Leu Val Val Ser Gly Asp
10435 10440 10445

Gly Leu Ala Arg Gly Tyr Thr Asn Ser Thr Leu Asn Ala Asp Arg Phe
10450 10455 10460

Val Asp Ile Val Ile Asn Asp Gln Lys Ala Arg Ala Tyr Arg Thr Gly
10465 10470 10475 10480

Asp Arg Thr Arg Tyr Arg Pro Lys Asp Gly Ser Ile Glu Phe Phe Gly
10485 10490 10495

Arg Met Asp Gln Gln Val Lys Ile Arg Gly His Arg Val Glu Pro Ala
10500 10505 10510

Glu Val Glu Gln Ala Met Leu Gly Asn Lys Ala Ile His Asp Ala Ala
10515 10520 10525

Val Val Val Gln Ala Val Asp Gly Gln Glu Thr Glu Met Ile Gly Phe
10530 10535 10540

Val Ser Met Ala Ser Asp Arg Phe Ser Glu Gly Glu Glu Glu Ile Thr
10545 10550 10555 10560

Asn Gln Val Gln Glu Trp Glu Asp His Phe Glu Ser Thr Ala Tyr Ala
10565 10570 10575

Gly Ile Glu Ala Ile Asp Gln Ala Thr Leu Gly Arg Asp Phe Thr Ser
10580 10585 10590

Trp Thr Ser Met Tyr Asn Gly Asn Leu Ile Asp Lys Ala Glu Met Glu
10595 10600 10605

Glu Trp Leu Asp Asp Thr Met Gln Ser Leu Leu Asp Lys Glu Asp Ala
10610 10615 10620

Arg Pro Cys Ala Glu Ile Gly Thr Gly Thr Gly Met Val Leu Phe Asn
10625 10630 10635 10640

Leu Pro Lys Asn Asp Gly Leu Glu Ser Tyr Val Gly Ile Glu Pro Ser
10645 10650 10655

Arg Ser Ala Ala Leu Phe Val Asp Lys Ala Ala Gln Asp Phe Pro Gly
10660 10665 10670

Leu Gln Gly Lys Thr Gln Ile Leu Val Gly Thr Ala Glu Asp Ile Lys
10675 10680 10685

Leu Val Lys Asp Phe His Pro Asp Val Val Val Ile Asn Ser Val Ala
10690 10695 10700

Gln Tyr Phe Pro Ser Arg Ser Tyr Leu Val Gln Ile Ala Ser Glu Leu
10705 10710 10715 10720

Ile His Met Thr Ser Val Lys Thr Ile Phe Phe Gly Asp Met Arg Ser
10725 10730 10735

Trp Ala Thr Asn Arg Asp Phe Leu Val Ser Arg Ala Leu Tyr Thr Leu
10740 10745 10750

Gly Asp Lys Ala Thr Lys Asp Gln Ile Arg Gln Glu Val Ala Arg Leu
10755 10760 10765

Glu Glu Asn Glu Asp Glu Leu Leu Val Asp Pro Ala Phe Phe Thr Ser
10770 10775 10780

Leu Thr Ser Gln Trp Pro Gly Lys Val Lys His Val Glu Ile Leu Pro
10785 10790 10795 10800

Lys Arg Met Arg Thr Ser Asn Glu Leu Ser Ser Tyr Arg Tyr Ala Ala
10805 10810 10815

Val Leu His Ile Cys Arg Asp Gly Glu Gly Arg Asn Arg Tyr Gly Arg
10820 10825 10830

Arg Val His Ser Val Glu Glu Asn Ala Trp Ile Asp Phe Ala Ser Ser
10835 10840 10845

Gly Met Asp Arg His Ala Leu Val Gln Met Leu Asp Glu Arg Arg Asp
10850 10855 10860

Ala Lys Thr Val Ala Ile Gly Asn Ile Pro His Ser Asn Thr Ile Asn
10865 10870 10875 10880

Glu Arg His Phe Thr Thr Ser Leu Asp Thr Glu Gly Glu Gly Ile Ala

10885 10890 10895

Gln Asp Ser Leu Asp Gly Ser Ala Trp Gln Ser Ala Thr Lys Ala Met
10900 10905 10910

Ala Ala Arg Cys Pro Cys Leu Ser Val Thr Glu Leu Val Glu Ile Gly
10915 10920 10925

Gln Ala Ala Gly Phe Arg Val Glu Val Ser Trp Ala Arg Gln Arg Ser
10930 10935 10940

Gln His Gly Ala Leu Asp Val Val Phe His His Leu Glu Asp Asp Arg
10945 10950 10955 10960

Val Gly Arg Val Leu Ile Asn Phe Pro Thr Asp Phe Glu Arg Leu Pro
10965 10970 10975

Pro Ser Thr Gly Leu Thr Ser Arg Pro Leu Gln Arg Ile Gln Asn Arg
10980 10985 10990

Arg Phe Glu Ser Gln Ile Arg Glu Gln Leu Gln Thr Leu Leu Pro Pro
10995 11000 11005

Tyr Met Val Pro Ser Arg Ile Val Val Leu Glu Arg Met Pro Leu Asn
11010 11015 11020

Ala Asn Ser Lys Val Asp Arg Lys Glu Leu Ala Arg Lys Ala Arg Thr
11025 11030 11035 11040

Leu Gln Thr Ile Lys Pro Ser Ala Thr Arg Val Ala Pro Arg Asn Asp
11045 11050 11055

Ile Glu Ala Val Leu Cys Asp Glu Phe Gln Ala Val Leu Gly Val Thr
11060 11065 11070

Val Gly Val Met Asp Asn Phe Phe Glu Leu Gly Gly His Ser Leu Met
11075 11080 11085

Ala Thr Lys Leu Ala Ala Arg Leu Ser Arg Arg Leu Asp Thr Arg Val
11090 11095 11100

Ser Val Lys Asp Ile Phe Asn Gln Pro Ile Leu Gln Asp Leu Ala Asp
11105 11110 11115 11120

Val Val Gln Thr Gly Ser Ala Pro His Glu Ala Ile Pro Ser Thr Pro
11125 11130 11135

Tyr Ser Gly Pro Val Glu Gln Ser Phe Ser Gln Gly Arg Leu Trp Phe
11140 11145 11150

Leu Asp Gln Leu Asn Leu Asn Ala Ser Trp Tyr His Met Pro Leu Ala
11155 11160 11165

Ser Arg Leu Arg Gly Pro Leu Arg Ile Glu Ala Leu Gln Ser Ala Leu
11170 11175 11180

Ala Thr Ile Glu Ala Arg His Glu Ser Leu Arg Thr Thr Phe Glu Glu
11185 11190 11195 11200

Gln Asp Gly Val Pro Val Gln Ile Val Arg Ala Ala Arg Asn Lys Gln
11205 11210 11215

Leu Arg Ile Ile Asp Val Ser Gly Thr Glu Asp Ala Tyr Leu Ala Ala
11220 11225 11230

Leu Lys Gln Glu Gln Asp Ala Ala Phe Asp Leu Thr Ala Glu Pro Gly
11235 11240 11245

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Trp Arg Val Ala Leu Leu Arg Leu Gly Pro Asp Asp His Val Leu Ser
    11250                11255                11260

Ile Val Met His His Ile Ile Ser Asp Gly Trp Ser Val Asp Ile Leu
11265                11270                11275                11280

Arg Gln Glu Leu Gly Gln Leu Tyr Ser Asn Ala Ser Ser Gln Pro Ala
                11285                11290                11295

Pro Leu Pro Ile Gln Tyr Arg Asp Phe Ala Ile Trp Gln Lys Gln Asp
            11300                11305                11310

Ser Gln Ile Ala Glu His Gln Lys Gln Leu Asn Tyr Trp Lys Arg Gln
        11315                11320                11325

Leu Val Asn Ser Lys Pro Ala Glu Leu Leu Ala Asp Phe Thr Arg Pro
    11330                11335                11340

Lys Ala Leu Ser Gly Asp Ala Asp Val Ile Pro Ile Glu Ile Asp Asp
11345                11350                11355                11360

Gln Val Tyr Gln Asn Leu Arg Ser Phe Cys Arg Ala Arg His Val Thr
                11365                11370                11375

Ser Phe Val Ala Leu Leu Ala Ala Phe Arg Ala Ala His Tyr Arg Leu
            11380                11385                11390

Thr Gly Ala Glu Asp Ala Thr Ile Gly Ser Pro Ile Ala Asn Arg Asn
        11395                11400                11405

Arg Pro Glu Leu Glu Gly Leu Ile Gly Cys Phe Val Asn Thr Gln Cys
    11410                11415                11420

Leu Arg Ile Pro Val Lys Ser Glu Asp Thr Phe Asp Thr Leu Val Lys
11425                11430                11435                11440

Gln Ala Arg Glu Thr Ala Thr Glu Ala Gln Asp Asn Gln Asp Val Pro
                11445                11450                11455

Phe Glu Arg Ile Val Ser Ser Met Val Ala Ser Ser Arg Asp Thr Ser
            11460                11465                11470

Arg Asn Pro Leu Val Gln Val Met Phe Ala Val His Ser Gln His Asp
        11475                11480                11485

Leu Gly Asn Ile Arg Leu Glu Gly Val Glu Gly Lys Pro Val Ser Met
    11490                11495                11500

Ala Ala Ser Thr Arg Phe Asp Ala Glu Met His Leu Phe Glu Asp Gln
11505                11510                11515                11520

Gly Met Leu Gly Gly Asn Val Val Phe Ser Lys Asp Leu Phe Glu Ser
                11525                11530                11535

Glu Thr Ile Arg Ser Val Val Ala Val Phe Gln Glu Thr Leu Arg Arg
            11540                11545                11550

Gly Leu Ala Asn Pro His Ala Asn Leu Ala Thr Leu Pro Leu Thr Asp
        11555                11560                11565

Gly Leu Pro Ser Leu Arg Ser Leu Cys Leu Gln Val Asn Gln Pro Asp
    11570                11575                11580

Tyr Pro Arg Asp Ala Ser Val Ile Asp Val Phe Arg Glu Gln Val Ala
11585                11590                11595                11600
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Ser Ile Pro Lys Ser Ile Ala Val Ile Asp Ala Ser Ser Gln Leu Thr
11605 11610 11615

Tyr Thr Glu Leu Asp Glu Arg Ser Ser Gln Leu Ala Thr Trp Leu Arg
11620 11625 11630

Arg Gln Val Thr Val Pro Glu Glu Leu Val Gly Val Leu Ala Pro Arg
11635 11640 11645

Ser Cys Glu Thr Ile Ile Ala Phe Leu Gly Ile Ile Lys Ala Asn Leu
11650 11655 11660

Ala Tyr Leu Pro Leu Asp Val Asn Ala Pro Ala Gly Arg Ile Glu Thr
11665 11670 11675 11680

Ile Leu Ser Ser Leu Pro Gly Asn Arg Leu Ile Leu Leu Gly Ser Asp
11685 11690 11695

Thr Gln Ala Val Lys Leu His Ala Asn Ser Val Arg Phe Thr Arg Ile
11700 11705 11710

Ser Asp Ala Leu Val Glu Ser Gly Ser Pro Pro Thr Glu Glu Leu Ser
11715 11720 11725

Thr Arg Pro Thr Ala Gln Ser Leu Ala Tyr Val Met Phe Thr Ser Gly
11730 11735 11740

Ser Thr Gly Val Pro Lys Gly Val Met Val Glu His Arg Gly Ile Thr
11745 11750 11755 11760

Arg Leu Val Lys Asn Ser Asn Val Val Ala Lys Gln Pro Ala Ala Ala
11765 11770 11775

Ala Ile Ala His Leu Ser Asn Ile Ala Phe Asp Ala Ser Ser Trp Glu
11780 11785 11790

Ile Tyr Ala Pro Leu Leu Asn Gly Gly Thr Val Val Cys Ile Asp Tyr
11795 11800 11805

Tyr Thr Thr Ile Asp Ile Lys Ala Leu Glu Ala Val Phe Lys Gln His
11810 11815 11820

His Ile Arg Gly Ala Met Leu Pro Pro Ala Leu Leu Lys Gln Cys Leu
11825 11830 11835 11840

Val Ser Ala Pro Thr Met Ile Ser Ser Leu Glu Ile Leu Phe Ala Ala
11845 11850 11855

Gly Asp Arg Leu Ser Ser Gln Asp Ala Ile Leu Ala Arg Arg Ala Val
11860 11865 11870

Gly Ser Gly Val Tyr Asn Ala Tyr Gly Pro Thr Glu Asn Thr Val Leu
11875 11880 11885

Ser Thr Ile His Asn Ile Gly Glu Asn Glu Ala Phe Ser Asn Gly Val
11890 11895 11900

Pro Ile Gly Asn Ala Val Ser Asn Ser Gly Ala Phe Val Met Asp Gln
11905 11910 11915 11920

Asn Gln Gln Leu Val Ser Ala Gly Val Ile Gly Glu Leu Val Val Thr
11925 11930 11935

Gly Asp Gly Leu Ala Arg Gly Tyr Thr Asp Ser Lys Leu Arg Val Asp
11940 11945 11950

Arg Phe Ile Tyr Ile Thr Leu Asp Gly Asn Arg Val Arg Ala Tyr Arg

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        11955                11960                11965

Thr Gly Asp Arg Val Arg His Arg Pro Lys Asp Gly Gln Ile Glu Phe
    11970                11975                11980

Phe Gly Arg Met Asp Gln Gln Ile Lys Ile Arg Gly His Arg Ile Glu
11985                11990                11995                12000

Pro Ala Glu Val Glu Gln Ala Leu Ala Arg Asp Pro Ala Ile Ser Asp
                12005                12010                12015

Ser Ala Val Ile Thr Gln Leu Thr Asp Glu Glu Glu Pro Glu Leu Val
            12020                12025                12030

Ala Phe Phe Ser Leu Lys Gly Asn Ala Asn Gly Thr Asn Gly Val Asn
        12035                12040                12045

Gly Val Ser Asp Gln Glu Lys Ile Asp Gly Asp Glu Gln His Ala Leu
    12050                12055                12060

Leu Met Glu Asn Lys Ile Arg His Asn Leu Gln Ala Leu Leu Pro Thr
12065                12070                12075                12080

Tyr Met Ile Pro Ser Arg Ile Ile His Val Asp Gln Leu Pro Val Asn
                12085                12090                12095

Ala Asn Gly Lys Ile Asp Arg Asn Glu Leu Ala Val Arg Ala Gln Ala
            12100                12105                12110

Thr Pro Arg Thr Ser Ser Val Ser Thr Tyr Val Ala Pro Arg Asn Asp
        12115                12120                12125

Ile Glu Thr Ile Ile Cys Lys Glu Phe Ala Asp Ile Leu Ser Val Arg
    12130                12135                12140

Val Gly Ile Thr Asp Asn Phe Phe Asp Leu Gly Gly His Ser Leu Ile
12145                12150                12155                12160

Ala Thr Lys Leu Ala Ala Arg Leu Ser Arg Arg Leu Asp Thr Arg Val
                12165                12170                12175

Ser Val Arg Asp Val Phe Asp Thr Pro Val Val Gly Gln Leu Ala Ala
            12180                12185                12190

Ser Ile Gln Gln Gly Ser Thr Pro His Glu Ala Ile Pro Ala Leu Ser
        12195                12200                12205

His Ser Gly Pro Val Gln Gln Ser Phe Ala Gln Gly Arg Leu Trp Phe
    12210                12215                12220

Leu Asp Arg Phe Asn Leu Asn Ala Ala Trp Tyr Ile Met Pro Phe Gly
12225                12230                12235                12240

Val Arg Leu Arg Gly Pro Leu Arg Val Asp Ala Leu Gln Thr Ala Leu
                12245                12250                12255

Arg Ala Leu Glu Glu Arg His Glu Leu Leu Arg Thr Thr Phe Glu Glu
            12260                12265                12270

Gln Asp Gly Val Gly Met Gln Ile Val His Ser Pro Arg Met Arg Asp
        12275                12280                12285

Ile Cys Val Val Asp Ile Ser Gly Ala Asn Glu Asp Leu Ala Lys Leu
    12290                12295                12300

Lys Glu Glu Gln Gln Ala Pro Phe Asn Leu Ser Thr Glu Val Ala Trp
12305                12310                12315                12320
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Arg Val Ala Leu Phe Lys Ala Gly Glu Asn His His Ile Leu Ser Ile
12325 12330 12335

Val Met His His Ile Ile Ser Asp Gly Trp Ser Val Asp Ile Phe Gln
12340 12345 12350

Gln Glu Leu Ala Gln Phe Tyr Ser Val Ala Val Arg Gly His Asp Pro
12355 12360 12365

Leu Ser Gln Val Lys Pro Leu Pro Ile His Tyr Arg Asp Phe Ala Val
12370 12375 12380

Trp Gln Arg Gln Asp Lys Gln Val Ala Val His Glu Ser Gln Leu Gln
12385 12390 12395 12400

Tyr Trp Ile Glu Gln Leu Ala Asp Ser Thr Pro Ala Glu Ile Leu Ser
12405 12410 12415

Asp Phe Asn Arg Pro Glu Val Leu Ser Gly Glu Ala Gly Thr Val Pro
12420 12425 12430

Ile Val Ile Glu Asp Glu Val Tyr Glu Lys Leu Ser Leu Phe Cys Arg
12435 12440 12445

Asn His Gln Val Thr Ser Phe Val Val Leu Leu Ala Ala Phe Arg Val
12450 12455 12460

Ala His Tyr Arg Leu Thr Gly Ala Glu Asp Ala Thr Ile Gly Thr Pro
12465 12470 12475 12480

Ile Ala Asn Arg Asn Arg Pro Glu Leu Glu Asp Leu Ile Gly Phe Phe
12485 12490 12495

Val Asn Thr Gln Cys Met Arg Ile Ala Leu Glu Glu His Asp Asn Phe
12500 12505 12510

Leu Ser Val Val Arg Arg Val Arg Ser Thr Ala Ala Ser Ala Phe Glu
12515 12520 12525

Asn Gln Asp Val Pro Phe Glu Arg Leu Val Ser Ala Leu Leu Pro Gly
12530 12535 12540

Ser Arg Asp Ala Ser Arg Asn Pro Leu Val Gln Leu Met Phe Val Val
12545 12550 12555 12560

His Ser Gln Arg Asn Leu Gly Lys Leu Gln Leu Glu Gly Leu Glu Gly
12565 12570 12575

Glu Pro Thr Pro Tyr Thr Ala Thr Thr Arg Phe Asp Val Glu Phe His
12580 12585 12590

Leu Phe Glu Gln Asp Lys Gly Leu Ala Gly Asn Val Val Phe Ala Ala
12595 12600 12605

Asp Leu Phe Glu Ala Ala Thr Ile Arg Ser Val Val Glu Val Phe His
12610 12615 12620

Glu Ile Leu Arg Arg Gly Leu Asp Gln Pro Asp Ile Ala Ile Ser Thr
12625 12630 12635 12640

Met Pro Leu Val Asp Gly Leu Ala Ala Leu Asn Ser Arg Asn Leu Pro
12645 12650 12655

Ala Val Glu Asp Ile Glu Pro Asp Phe Ala Thr Glu Ala Ser Val Val
12660 12665 12670

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Asp Val Phe Gln Thr Gln Val Val Ala Asn Pro Asp Ala Leu Ala Val
        12675                12680                12685

Thr Asp Thr Ser Thr Lys Leu Thr Tyr Ala Glu Leu Asp Gln Gln Ser
    12690                12695                12700

Asp His Val Ala Ala Trp Leu Ser Lys Gln Lys Leu Pro Ala Glu Ser
12705                12710                12715                12720

Ile Val Val Val Leu Ala Pro Arg Ser Ser Glu Thr Ile Val Ala Cys
                12725                12730                12735

Ile Gly Ile Leu Lys Ala Asn Leu Ala Tyr Leu Pro Met Asp Ser Asn
            12740                12745                12750

Val Pro Glu Ala Arg Arg Gln Ala Ile Leu Ser Glu Ile Pro Gly Glu
        12755                12760                12765

Lys Phe Val Leu Leu Gly Ala Gly Val Pro Ile Pro Asp Asn Lys Thr
    12770                12775                12780

Ala Asp Val Arg Met Val Phe Ile Ser Asp Ile Val Ala Ser Lys Thr
12785                12790                12795                12800

Asp Lys Ser Tyr Ser Pro Gly Thr Arg Pro Ser Ala Ser Ser Leu Ala
                12805                12810                12815

Tyr Val Ile Phe Thr Ser Gly Ser Thr Gly Arg Pro Lys Gly Val Met
            12820                12825                12830

Val Glu His Arg Gly Val Ile Ser Leu Val Lys Gln Asn Ala Ser Arg
        12835                12840                12845

Ile Pro Gln Ser Leu Arg Met Ala His Val Ser Asn Leu Ala Phe Asp
    12850                12855                12860

Ala Ser Val Trp Glu Ile Phe Thr Thr Leu Leu Asn Gly Gly Thr Leu
12865                12870                12875                12880

Phe Cys Ile Ser Tyr Phe Thr Val Leu Asp Ser Lys Ala Leu Ser Ala
                12885                12890                12895

Ala Phe Ser Asp His Arg Ile Asn Ile Thr Leu Leu Pro Pro Ala Leu
            12900                12905                12910

Leu Lys Gln Cys Leu Ala Asp Ala Pro Ser Val Leu Ser Ser Leu Glu
        12915                12920                12925

Ser Leu Tyr Ile Gly Gly Asp Arg Leu Asp Gly Ala Asp Ala Thr Lys
    12930                12935                12940

Val Lys Asp Leu Val Lys Gly Lys Ala Tyr Asn Ala Tyr Gly Pro Thr
12945                12950                12955                12960

Glu Asn Ser Val Met Ser Thr Ile Tyr Thr Ile Glu His Glu Thr Phe
                12965                12970                12975

Ala Asn Gly Val Pro Ile Gly Thr Ser Leu Gly Pro Lys Ser Lys Ala
            12980                12985                12990

Tyr Ile Met Asp Gln Asp Gln Gln Leu Val Pro Ala Gly Val Met Gly
        12995                13000                13005

Glu Leu Val Val Ala Gly Asp Gly Leu Ala Arg Gly Tyr Thr Asp Pro
    13010                13015                13020

Ser Leu Asn Thr Gly Arg Phe Ile His Ile Thr Ile Asp Gly Lys Gln
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13025 13030 13035 13040

Val Gln Ala Tyr Arg Thr Gly Asp Arg Val Arg Tyr Arg Pro Arg Asp
13045 13050 13055

Tyr Gln Ile Glu Phe Phe Gly Arg Leu Asp Gln Gln Ile Lys Ile Arg
13060 13065 13070

Gly His Arg Ile Glu Pro Ala Glu Val Glu Gln Ala Leu Leu Ser Asp
13075 13080 13085

Ser Ser Ile Asn Asp Ala Val Val Val Ser Ala Gln Asn Lys Glu Gly
13090 13095 13100

Leu Glu Met Val Gly Tyr Ile Thr Thr Gln Ala Ala Gln Ser Val Asp
13105 13110 13115 13120

Lys Glu Glu Ala Ser Asn Lys Val Gln Glu Trp Glu Ala His Phe Asp
13125 13130 13135

Ser Thr Ala Tyr Ala Asn Ile Gly Gly Ile Asp Arg Asp Ala Leu Gly
13140 13145 13150

Gln Asp Phe Leu Ser Trp Thr Ser Met Tyr Asp Gly Ser Leu Ile Pro
13155 13160 13165

Arg Glu Glu Met Gln Glu Trp Leu Asn Asp Thr Met Arg Ser Leu Leu
13170 13175 13180

Asp Asn Gln Pro Pro Gly Lys Val Leu Glu Ile Gly Thr Gly Thr Gly
13185 13190 13195 13200

Met Val Leu Phe Asn Leu Gly Lys Val Glu Gly Leu Gln Ser Tyr Ala
13205 13210 13215

Gly Leu Glu Pro Ser Arg Ser Val Thr Ala Trp Val Asn Lys Ala Ile
13220 13225 13230

Glu Thr Phe Pro Ser Leu Ala Gly Ser Ala Arg Val His Val Gly Thr
13235 13240 13245

Ala Glu Asp Ile Ser Ser Ile Asp Gly Leu Arg Ser Asp Leu Val Val
13250 13255 13260

Ile Asn Ser Val Ala Gln Tyr Phe Pro Ser Arg Glu Tyr Leu Ala Glu
13265 13270 13275 13280

Leu Thr Ala Asn Leu Ile Arg Leu Pro Gly Val Lys Arg Ile Phe Phe
13285 13290 13295

Gly Asp Met Arg Thr Tyr Ala Thr Asn Lys Asp Phe Leu Val Ala Arg
13300 13305 13310

Ala Val His Thr Leu Gly Ser Asn Ala Ser Lys Ala Met Val Arg Gln
13315 13320 13325

Gln Val Ala Lys Leu Glu Asp Asp Glu Glu Glu Leu Leu Val Asp Pro
13330 13335 13340

Ala Phe Phe Thr Ser Leu Ser Asp Gln Phe Pro Asp Glu Ile Lys His
13345 13350 13355 13360

Val Glu Ile Leu Pro Lys Arg Met Ala Ala Thr Asn Glu Leu Ser Ser
13365 13370 13375

Tyr Arg Tyr Ala Ala Val Ile His Val Gly Gly His Gln Met Pro Asn
13380 13385 13390

Gly Glu Asp Glu Asp Lys Gln Trp Ala Val Lys Asp Ile Asn Pro Lys
13395 13400 13405

Ala Trp Val Asp Phe Ala Gly Thr Arg Met Asp Arg Gln Ala Leu Leu
13410 13415 13420

Gln Leu Leu Gln Asp Arg Gln Arg Gly Asp Asp Val Val Ala Val Ser
13425 13430 13435 13440

Asn Ile Pro Tyr Ser Lys Thr Ile Met Glu Arg His Leu Ser Gln Ser
13445 13450 13455

Leu Asp Asp Asp Glu Asp Gly Thr Ser Ala Val Asp Gly Thr Ala Trp
13460 13465 13470

Ile Ser Arg Thr Gln Ser Arg Ala Lys Glu Cys Pro Ala Leu Ser Val
13475 13480 13485

Ala Asp Leu Ile Glu Ile Gly Lys Gly Ile Gly Phe Glu Val Glu Ala
13490 13495 13500

Ser Trp Ala Arg Gln His Ser Gln Arg Gly Gly Leu Asp Ala Val Phe
13505 13510 13515 13520

His Arg Phe Glu Pro Pro Arg His Ser Gly His Val Met Phe Arg Phe
13525 13530 13535

Pro Thr Glu His Lys Gly Arg Ser Ser Ser Ser Leu Thr Asn Arg Pro
13540 13545 13550

Leu His Leu Leu Gln Ser Arg Arg Leu Glu Ala Lys Val Arg Glu Arg
13555 13560 13565

Leu Gln Ser Leu Leu Pro Pro Tyr Met Ile Pro Ser Arg Ile Thr Leu
13570 13575 13580

Leu Asp Gln Met Pro Leu Thr Ser Asn Gly Lys Val Asp Arg Lys Lys
13585 13590 13595 13600

Leu Ala Arg Gln Ala Arg Val Ile Pro Arg Ser Ala Ala Ser Thr Leu
13605 13610 13615

Asp Phe Val Ala Pro Arg Thr Glu Ile Glu Val Val Leu Cys Glu Glu
13620 13625 13630

Phe Thr Asp Leu Leu Gly Val Lys Val Gly Ile Thr Asp Asn Phe Phe
13635 13640 13645

Glu Leu Gly Gly His Ser Leu Leu Ala Thr Lys Leu Ser Ala Arg Leu
13650 13655 13660

Ser Arg Arg Leu Asp Ala Gly Ile Thr Val Lys Gln Val Phe Asp Gln
13665 13670 13675 13680

Pro Val Leu Ala Asp Leu Ala Ala Ser Ile Leu Gln Gly Ser Ser Arg
13685 13690 13695

His Arg Ser Ile Pro Ser Leu Pro Tyr Glu Gly Pro Val Glu Gln Ser
13700 13705 13710

Phe Ala Gln Gly Arg Leu Trp Phe Leu Asp Gln Phe Asn Ile Asp Ala
13715 13720 13725

Leu Trp Tyr Leu Ile Pro Phe Ala Leu Arg Met Arg Gly Pro Leu Gln
13730 13735 13740

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Val Asp Ala Leu Ala Ala Ala Leu Val Ala Leu Glu Glu Arg His Glu
13745                 13750                 13755                 13760

Ser Leu Arg Thr Thr Phe Glu Glu Arg Asp Gly Val Gly Ile Gln Val
                    13765                 13770                 13775

Val Gln Pro Leu Arg Thr Thr Lys Asp Ile Arg Ile Ile Asp Val Ser
                13780                 13785                 13790

Gly Met Arg Asp Asp Asp Ala Tyr Leu Glu Pro Leu Gln Lys Glu Gln
        13795                 13800                 13805

Gln Thr Pro Phe Asp Leu Ala Ser Glu Pro Gly Trp Arg Val Ala Leu
    13810                 13815                 13820

Leu Lys Leu Gly Lys Asp Asp His Ile Leu Ser Ile Val Met His His
13825                 13830                 13835                 13840

Ile Ile Ser Asp Gly Trp Ser Thr Glu Val Leu Gln Arg Glu Leu Gly
                    13845                 13850                 13855

Gln Phe Tyr Leu Ala Ala Lys Ser Gly Lys Ala Pro Leu Ser Gln Val
                13860                 13865                 13870

Ala Pro Leu Pro Ile Gln Tyr Arg Asp Phe Ala Val Trp Gln Arg Gln
        13875                 13880                 13885

Glu Glu Gln Val Ala Glu Ser Gln Arg Gln Leu Asp Tyr Trp Lys Lys
    13890                 13895                 13900

Gln Leu Ala Asp Ser Ser Pro Ala Glu Leu Leu Ala Asp Tyr Thr Arg
13905                 13910                 13915                 13920

Pro Asn Val Leu Ser Gly Glu Ala Gly Ser Val Ser Phe Val Ile Asn
                    13925                 13930                 13935

Asp Ser Val Tyr Lys Ser Leu Val Ser Phe Cys Arg Ser Arg Gln Val
                13940                 13945                 13950

Thr Thr Phe Thr Thr Leu Leu Ala Ala Phe Arg Ala Ala His Tyr Arg
        13955                 13960                 13965

Met Thr Gly Ser Asp Asp Ala Thr Ile Gly Thr Pro Ile Ala Asn Arg
    13970                 13975                 13980

Asn Arg Pro Glu Leu Glu Asn Leu Ile Gly Cys Phe Val Asn Thr Gln
13985                 13990                 13995                 14000

Cys Met Arg Ile Thr Ile Gly Asp Asp Glu Thr Phe Glu Ser Leu Val
                    14005                 14010                 14015

Gln Gln Val Arg Ser Thr Thr Ala Thr Ala Phe Glu Asn Gln Asp Val
                14020                 14025                 14030

Pro Phe Glu Arg Ile Val Ser Thr Leu Ser Ala Gly Ser Arg Asp Thr
        14035                 14040                 14045

Ser Arg Asn Pro Leu Val Gln Leu Leu Phe Ala Val His Ser Gln Gln
    14050                 14055                 14060

Gly Leu Gly Arg Ile Gln Leu Asp Gly Val Val Asp Glu Pro Val Leu
14065                 14070                 14075                 14080

Ser Thr Val Ser Thr Arg Phe Asp Leu Glu Phe His Ala Phe Gln Glu
                    14085                 14090                 14095

Ala Asp Arg Leu Asn Gly Ser Val Met Phe Ala Thr Asp Leu Phe Gln
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14100 14105 14110

Pro Glu Thr Ile Gln Gly Phe Val Ala Val Val Glu Glu Val Leu Gln
14115 14120 14125

Arg Gly Leu Glu Gln Pro Gln Ser Pro Ile Ala Thr Met Pro Leu Ala
14130 14135 14140

Glu Gly Ile Ala Gln Leu Arg Asp Ala Gly Ala Leu Gln Met Pro Lys
14145 14150 14155 14160

Ser Asp Tyr Pro Arg Asn Ala Ser Leu Val Asp Val Phe Gln Gln Gln
14165 14170 14175

Ala Met Ala Ser Pro Ser Thr Val Ala Val Thr Asp Ser Thr Ser Lys
14180 14185 14190

Leu Thr Tyr Ala Glu Leu Asp Arg Leu Ser Asp Gln Ala Ala Ser Tyr
14195 14200 14205

Leu Arg Arg Gln Gln Leu Pro Ala Glu Thr Met Val Ala Val Leu Ala
14210 14215 14220

Pro Arg Ser Cys Glu Thr Ile Ile Ala Phe Leu Ala Ile Leu Lys Ala
14225 14230 14235 14240

Asn Leu Ala Tyr Met Pro Leu Asp Val Asn Thr Pro Ser Ala Arg Met
14245 14250 14255

Glu Ala Ile Ile Ser Ser Val Pro Gly Arg Arg Leu Ile Leu Val Gly
14260 14265 14270

Ser Gly Val Arg His Ala Asp Ile Asn Val Pro Asn Ala Lys Thr Met
14275 14280 14285

Leu Ile Ser Asp Thr Val Thr Gly Thr Asp Ala Ile Gly Thr Pro Glu
14290 14295 14300

Pro Leu Val Val Arg Pro Ser Ala Thr Ser Leu Ala Tyr Val Ile Phe
14305 14310 14315 14320

Thr Ser Gly Ser Thr Gly Lys Pro Lys Gly Val Met Val Glu His Arg
14325 14330 14335

Ala Ile Met Arg Leu Val Lys Asp Ser Asn Val Val Thr His Met Pro
14340 14345 14350

Pro Ala Thr Arg Met Ala His Val Thr Asn Ile Ala Phe Asp Val Ser
14355 14360 14365

Leu Phe Glu Met Cys Ala Thr Leu Leu Asn Gly Gly Thr Leu Val Cys
14370 14375 14380

Ile Asp Tyr Leu Thr Leu Leu Asp Ser Thr Met Leu Arg Glu Thr Phe
14385 14390 14395 14400

Glu Arg Glu Gln Val Arg Ala Ala Ile Phe Pro Pro Ala Leu Leu Arg
14405 14410 14415

Gln Cys Leu Val Asn Met Pro Asp Ala Ile Gly Met Leu Glu Ala Val
14420 14425 14430

Tyr Val Ala Gly Asp Arg Phe His Ser Arg Asp Ala Arg Ala Thr Gln
14435 14440 14445

Ala Leu Ala Gly Pro Arg Val Tyr Asn Ala Tyr Gly Pro Thr Glu Asn
14450 14455 14460

Ala Ile Leu Ser Thr Ile Tyr Asn Ile Asp Lys His Asp Pro Tyr Val
14465 14470 14475 14480

Asn Gly Val Pro Ile Gly Ser Ala Val Ser Asn Ser Gly Ala Tyr Val
14485 14490 14495

Met Asp Arg Asn Gln Gln Leu Leu Pro Pro Gly Val Met Gly Glu Leu
14500 14505 14510

Val Val Thr Gly Glu Gly Val Ala Arg Gly Tyr Thr Asp Ala Ser Leu
14515 14520 14525

Asp Thr Asp Arg Phe Val Thr Val Thr Ile Asp Gly Gln Arg Gln Arg
14530 14535 14540

Ala Tyr Arg Thr Gly Asp Arg Val Arg Tyr Arg Pro Lys Gly Phe Gln
14545 14550 14555 14560

Ile Glu Phe Phe Gly Arg Leu Asp Gln Gln Ala Lys Ile Arg Gly His
14565 14570 14575

Arg Val Glu Leu Gly Glu Val Glu His Ala Leu Leu Ser Glu Asn Ser
14580 14585 14590

Val Thr Asp Ala Ala Val Val Leu Arg Thr Met Glu Glu Glu Asp Pro
14595 14600 14605

Gln Leu Val Ala Phe Val Thr Thr Asp His Glu Tyr Arg Ser Gly Ser
14610 14615 14620

Ser Asn Glu Glu Glu Asp Pro Tyr Ala Thr Gln Ala Ala Gly Asp Met
14625 14630 14635 14640

Arg Lys Arg Leu Arg Ser Leu Leu Pro Tyr Tyr Met Val Pro Ser Arg
14645 14650 14655

Val Thr Ile Leu Arg Gln Met Pro Leu Asn Ala Asn Gly Lys Val Asp
14660 14665 14670

Arg Lys Asp Leu Ala Arg Arg Ala Gln Met Thr Pro Thr Ala Ser Ser
14675 14680 14685

Ser Gly Pro Val His Val Ala Pro Arg Asn Glu Thr Glu Ala Ala Ile
14690 14695 14700

Cys Asp Glu Phe Glu Thr Ile Leu Gly Val Lys Val Gly Ile Thr Asp
14705 14710 14715 14720

Asn Phe Phe Glu Leu Gly Gly His Ser Leu Leu Ala Thr Lys Leu Ala
14725 14730 14735

Ala Arg Leu Ser Arg Arg Met Gly Leu Arg Ile Ser Val Lys Asp Leu
14740 14745 14750

Phe Asp Asp Pro Val Pro Val Ser Leu Ala Gly Lys Leu Glu Gln Gln
14755 14760 14765

Gln Gly Phe Ser Gly Glu Asp Glu Ser Ser Thr Val Gly Ile Val Pro
14770 14775 14780

Phe Gln Leu Leu Pro Ala Glu Met Ser Arg Glu Ile Ile Gln Arg Asp
14785 14790 14795 14800

Val Val Pro Gln Ile Glu Asn Gly His Ser Thr Pro Leu Asp Met Tyr
14805 14810 14815

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Pro Ala Thr Gln Thr Gln Ile Phe Phe Leu His Asp Lys Ala Thr Gly
            14820               14825               14830

His Pro Ala Thr Pro Pro Leu Phe Ser Leu Asp Phe Pro Glu Thr Ala
        14835               14840               14845

Asp Cys Arg Arg Leu Ala Ser Ala Cys Ala Ala Leu Val Gln His Phe
    14850               14855               14860

Asp Ile Phe Arg Thr Val Phe Val Ser Arg Gly Gly Arg Phe Tyr Gln
14865               14870               14875               14880

Val Val Leu Ala His Leu Asp Val Pro Val Glu Val Ile Glu Thr Glu
                14885               14890               14895

Gln Glu Leu Asp Glu Val Ala Leu Ala Leu His Glu Ala Asp Lys Gln
            14900               14905               14910

Gln Pro Leu Arg Leu Gly Arg Ala Met Leu Arg Ile Ala Ile Leu Lys
        14915               14920               14925

Arg Pro Gly Ala Lys Met Arg Leu Val Leu Arg Met Ser His Ser Leu
    14930               14935               14940

Tyr Asp Gly Leu Ser Leu Glu His Ile Val Asn Ala Leu His Ala Leu
14945               14950               14955               14960

Tyr Ser Asp Lys His Leu Ala Gln Ala Pro Lys Phe Gly Leu Tyr Met
                14965               14970               14975

His His Met Ala Ser Arg Arg Ala Glu Gly Tyr Asn Phe Trp Arg Ser
            14980               14985               14990

Ile Leu Gln Gly Ser Ser Met Thr Ser Leu Lys Arg Ser Val Gly Ala
        14995               15000               15005

Leu Glu Ala Met Thr Pro Ser Ala Gly Thr Trp Gln Thr Ser Lys Ser
    15010               15015               15020

Ile Arg Ile Pro Pro Ala Ala Leu Lys Asn Gly Ile Thr Gln Ala Thr
15025               15030               15035               15040

Leu Phe Thr Ala Ala Val Ser Leu Leu Leu Ala Lys His Thr Lys Ser
                15045               15050               15055

Thr Asp Val Val Phe Gly Arg Val Val Ser Gly Arg Gln Asp Leu Ser
            15060               15065               15070

Ile Asn Cys Gln Asp Ile Val Gly Pro Cys Ile Asn Glu Val Pro Val
        15075               15080               15085

Arg Val Arg Ile Asp Glu Gly Asp Asp Met Gly Gly Leu Leu Arg Ala
    15090               15095               15100

Ile Gln Asp Gln Tyr Thr Ser Ser Phe Arg His Glu Thr Leu Gly Leu
15105               15110               15115               15120

Gln Glu Val Lys Glu Asn Cys Thr Asp Trp Thr Asp Ala Thr Lys Glu
                15125               15130               15135

Phe Ser Cys Cys Ile Ala Phe Gln Asn Leu Asn Leu His Pro Glu Ala
            15140               15145               15150

Glu Ile Glu Gly Gln Gln Ile Arg Leu Glu Gly Leu Pro Ala Lys Asp
        15155               15160               15165

Gln Ala Arg Gln Ala Asn Gly His Ala Pro Asn Gly Thr Asn Gly Thr
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15170 15175 15180

Asn Gly Thr Asn Gly Thr Asn Gly Ala Asn Gly Thr Asn Gly Thr Asn
15185 15190 15195 15200

Gly Thr Asn Gly Thr His Ala Asn Gly Ile Asn Gly Ser Asn Gly Val
15205 15210 15215

Asn Gly Arg Asp Ser Asn Val Val Ser Ala Ala Gly Asp Gln Ala Pro
15220 15225 15230

Val His Asp Leu Asp Ile Val Gly Ile Pro Glu Pro Asp Gly Ser Val
15235 15240 15245

Lys Ile Gly Ile Gly Ala Ser Arg Gln Ile Leu Gly Glu Lys Val Val
15250 15255 15260

Gly Ser Met Leu Asn Glu Leu Cys Glu Thr Met Leu Ala Leu Ser Arg
15265 15270 15275 15280

Thr

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 178 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Tolypocladium geodes

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

ATGCAACTAT CGGCTCTCCA ATTGCGAACA GAAATCGAGC AGAGCTTGAG GGCCTTATTG 60

GCTGTTTTGT GAATACTCAG TGTATGAGAC TGCCAGTTAC CGATGAAGAT ACATTCGCCA 120

ATTTGATTGA CTGTGTACGA GAGACGTCAA CCGAGGCCTT GAGCACCAAG ATATCCTT 178

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1713 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Neocosmospora vasinfecta

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

ACATCGGGGG TATTGATCGC GATGCCCTCG GACAGGACTT CTTATCCTGG ACATCCATGT 60

ACGACGGCTC ATTGATTCCC CGGGAAGAGA TGCAGGAATG GCTCAGCGAC ACTATGCACT 120

CACTCCTCGA CAACCAGCCA CCCGGAAGAG TGCTCGAGAT CGGAACTGGT ACCGGTATGG 180

TGCTTTTCAA TCTCGGCAAG GTTGAGGGAC TACAGAGCTA TGCCGGTCTT GAGCCCTCGC 240

GCTCCGTCAC TGCCTGGGTT AACAAGGCAA TCGAAACTTT CCCAAGCCTG GCAGGAAGCG 300

CCCGAGTCCA CGTTGGAACC GCCGAGGATG TCAGCTCCAT CAATGGACTG CGTGCCGATC 360

TCGTTGTGAT CAACTCGGTC GCCCAATACT TCCCAAGTCG AGAATATCTC GCTGAGCTGA 420

CGGCCAACTT GATTCGACTG CCCGGCGTCA AGCGTATTTT CTTCGGCGAC ATGAGAACCT 480

ATGCCACCAA TAAGGACTTC TTGGTGGCAC GAGCAGTCCA TACCCTAGGG TCCAATGCAT 540

CTAAGGCCAT GGTTCGACAA CAGGTGGCCA AGCTTGAAGA TGACGAGGAA GAGTTGCTTG 600

TTGACCCTGC CTTCTTCACC AGCCTGAGCG ACCAGTTCCC TGACGAAATC AAGCACGTCG 660

AGATTCTGCC AAAGAGGATG GCCGCGACCA ACGAACTCAG CTCTTACCGA TATGCTGCTG 720

TTATTCATGT GGGAGGCCAC GAGATGCCGA ATGGGGAGGA TGAGGATAAG CAATGGGCTG 780

TCAAGGATAT CGATCCGAAG GCCTGGGTGG ACTTCGCCGG CACGAGGATG GACCGTCAGG 840

CTCTCTTGCA GCTCCTCCAG GACCGCCAAC GTGGCGATGA CGTTGTTGCC GTCAGTAACA 900

TCCCATACAG CAAGACCATC ATGGAGCGCC ATCTGTCTCA GTCACTTGAC GATGACGAGG 960

ACGGCACTTC AGATGCAGAC GGAACGGCCT GGATATCGGC CACTCAATCA CGGGCGAAGG 1020

AATGCCCTGC TCTCTCAGTG GCCGACCTGA TTGAGATTGG TAAGGGGATC GGCTTCCAAG 1080

TTGAGACCAG CTGGGCTCGA CAACACTCCC AGCGCGGCGG ACTCGATGCT GTTTTCCACC 1140

GATTCGAAAA ACCAAGACAC TCGGGTCATG TCATGTTCAG GTTCCCAACT GAACACAAGG 1200

GGCCGGTCTT CGAGCAGTCT CACGAATCGC CCGCTACACC TGGTTCAGAG CCGCCGGCTG 1260

GAGGCAAAGG TCCGCGAGCG GCTGCAATCG CTGCTTCCAT CGTACATGAT TCCCTCTCGG 1320

ATCATGTTGC TCGATCAGAT GCCTCTCACG TCCAACGGCA AGGTGGATCG CAAGAAGCTC 1380

GCTCGACAAG CCCGGGTCAT CCCAACAATT GCCGCAAGCA CGTTGGACTT TGTGGCGCGC 1440

ACGCACGGAA ATCGAGGTCG GTTCTCTGCG AAGAATTTAC CGATCTACTA GGCGTCAAGG 1500

TCGGCATTAC AGACAACTTC TTCGAGTTGG GCGGCCATTC GCTGCTGGCC ACGAAACTGA 1560

GCGCACGTCT AAGTCGCAGA CTGGACGCCG GTGTCACTGT GAAGCAGATC TTTGACCAGC 1620

CAGTACTTGC TGATCTTGCT GCTTCTATTC GTCAAGGCTC GTCCCGTCAC AGGTCTATCC 1680

CGTCTTTACC CTACGAAGGA CCCGTGGAGC AGT 1713

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 655 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
(A) ORGANISM: Tolypocladium niveum
(B) STRAIN: ATCC 34921

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

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CATCAGCAAT CATGGGCAAC AAAGTCTTCT TCGACATTGA GTGGGAGGGC CCCGTCATGC      60
AGGGTTGCAA GCCTACCTCT ACCGTCAAAG AGCAGTCTGG TCGCATCAAC TTCAAGCTGT     120
ACGATGACGT CGTCCCCAAG ACCGCCGAGA ACTTCCGCGC TCTCTGCACC GGCGAGAAGG     180
GCTTCGGCTA CGAGGGCTCG TCCTTCCACC GTATCATCCC CGAGTTCATG CTCCAGGGCG     240
GCGACTTCAC CCGCGGTAAC GGCACTGGCG GCAAGTCCAT CTACGGCGAG AAGTTTGCCG     300
ATGAGAACTT CCAGCTGAAG CACGACCGCC CCGGTCTGCT GTCCATGGCT AACGCTGGCC     360
CCAACACCAA CGGCTCCCAG TTCTTCGTCA CCACCGTCGT CACCTCGTGG CTCAACGGCC     420
ACCACGTCGT CTTCGGCGAG GTCGCTGACC AGGAGTCCCT GGACGTCGTC AAGGCCCTTG     480
AGGCCACTGG CTCTGGTAGC GGCGCTGTCA AGTACAACAA GCGCGCCACC ATTGTCAAGT     540
CTGGCGAGCT GTAAGCTATG GCATCTGTGT ATCTTGCGAT TTCCTGCACC CAATTCGGAC     600
GGACAAAAGA GGCGCTGCCC ACAGCAAGGA CCTTTGGTTC ACGGGACGGC TTGAA          655
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

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GGGATATCGT GAATTGTAAT ACGACTCACT ATA                                   33
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(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2157 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iii) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GGATCCGTGA ATTGTAATAC GACTCACTAT AGGGCGAATT CGCTCGACGT CACCTAGGAG 60

ATCAGCCAGC TCCTTGGCCC TGTTCCGCAC GTTGATGCCC TGGTCTTTGC CGTTTGGATC 120

GATGAAGTGG AACTGGCGCA GCATCTTCAA AAGTGTGATG TGTCCCCGAG CGTCATCAAT 180

CACACGCTCA GAGCCATGCT TGACGAGGAA CTCGAGCAGT TGCAGAGCCT TGTAGATCTG 240

GCGCCACTCC TCGGCCGACT TCTCCGTGAA CCGTCGATAT ATCATCGGCA TGATCTCGTT 300

GAGGGTTTGG CTGGTTCTGT TAGCTGAAGC CGGGCTGTTC AGTCGTCGAA CCGCGTACTA 360

GTTGAAGGTG CCATTGGCAA TCTCCTGCAT AATACTGGAC GATGCTCCCC ATGGCTCGTT 420

GTTCGTTGCC TCTCGGACCT AGTACACGGA GTTAGCCACC GTGTTAACAA ACCGTCGCGG 480

CCGCAGACTA ACCTTGGACT CCATCTCGGT ATAGTTCATA ACAGCTACAT GCCAGGTCAG 540

CATTGGACGC GCCAGGGCTG AGGTCAGGCC TGGTACCATT TTGCGCCTTT CGGAACCCAG 600

CCTTGAGGTC GTACAAGGTC AGGTTGGAGA CTGTGTTCTT GATGTCGTTC AAGTCCATTT 660

TGGCAGATTC GACTTAGCGA GACCGGCCGG GAGCGGCAGA GGAGTTGTCG ATTCAGCACG 720

AGTCGCTGAT GAGCGATGGT TGTGGTGCAA GTCGATGGTC CGAGGGCGGG TGGTAGAGGT 780

GCTTGTCGCG ATGGACAGCT GGACTTTCGG GCCGCCAGCG ACACCTACCC GGCCTTGATG 840

GGTCAGAGGG ATGATCACGT GATATGGGTC GGAGTCGCAT CGTACTTCGT ACCAGCATCA 900

TCTCCAAGCC AGAGGCAGCA GAGATTATAT GACTGCAAAT GTGAAACGAA ATAAACCGTC 960

AATATGGTAT TTATGTTGGC AATTGCATGA TGCATCCCGG TGGAATTGAA CTAGAACGTC 1020

GAGGGCTTGC ATACCAGAGG CTGCGGGTGC ATCGTGGGCA GCGGTACCTG AGACTTCAGG 1080

CCAGAACGAC TGCTAATAAG CCGCGACGGA GCCAAAACTT TTCCCCTTTC CAGAGGCTCT 1140

CAGCTTTCGA CTCAGCCATT TGAACTTGCG ACTCAAGCCC GTTCATAACA CTTCATCTCT 1200

TGTACTTCTA CCGCATTACC TCCTGTACGA ATTGTAATCC CAGGTATGTC TATTTTCCTG 1260

TTGTTCTCGT CACATGCCCT CCCCAGCATG CGCAATGTCT TTGGACAACG CAGCTCCTCT 1320

CGACACATCA CAAAGGCTTC ACCCAGCAGA GCACGCGAGA GCCTGCGCGC GACAGCCTGC 1380

GAGCGACATG CAGCGCTTCC CTGGAAGCCA ACTGCACCAG CCTGGAAAGT TGCGCAGTTT 1440

GCCAGGGGGC CTCCGTCCCC CAGAATGGAT GGCACTCCTC GGCTTGACCT GGAGCGCTGC 1500

TCCCGATCAA GCCAGAGCCC GCCGGCGATG GGGACTGGCC GCGCCAGCCT CTGCACATGA 1560

GTGTGCTGGT TGGCTGGAGG TGGGTGGCCT TTGGCCTCCC AACCAGTCCC CACCATTTGC 1620

TGGAAGCTGC TGCAGCTGGT CGGAACGCAC CCAAGCCGTT GAGCTCAGCG CTCTGTCGGG 1680

TCGAGCGCCC ATTGGGGTTC CCGCGAAGGT CCTTTGACTG GGCCGGGGCC ACTCGTCTTG 1740

CCGGCCAGAG CTGAGCTCGC TGGTCTGGCA GCGACAGCAG CCGGGAGCTC CGTTGTCTAG 1800

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GCGATGAGCG CAGCGGCCAG AGCTCCGGGC CGGATCGGTG ACCTCACAGC CGTGGAAGCT    1860
CCTGGGCCCC CGAATCAAGG ACCGCAATTC CACGTGACTG GCCGGTTGCT CCCCTTCCGG    1920
CATTGCCCGC CCCGCTATTA CACCCCTTTG CGCGCCCTGG TTGGTTCAAA GTCCCACCGC    1980
TAACTTTTAA CCCCTCCAGC AGCCTTCAAA ATGAAGTCAA CGCTCCTTCG ACCCCTCCTA    2040
CCCCGCTATA AGCTCTGCTC CCCCGGGTCA AGATCTTTCC CTCTTCCACA ACTTGCATCA    2100
GCTTCCAACA CATTCCGAGC TGCTCGATTC TTCTCCGCAA CATCAGCAAT CATCGAT       2157
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Claims

1. An isolated DNA sequence which codes for an enzyme having cyclosporin synthetase-like activity.

2. A DNA sequence according to claim 1 which codes for cyclosporin synthetase or an enzyme that is at least 70% homologous thereto and that has cyclosporin synthetase-like activity.

3. A DNA sequence according to claim 1 or claim 2 which codes for an enzyme that has cyclosporin synthetase-like activity and in which at least one amino-acid recognition unit is different from that of cyclosporin synthetase.

4. A DNA sequence according to any of claims 1 to 3 which includes the 2890 bp SalI restriction fragment containing sequences 40239 to 43129 of Seq Id 1, or a sequence which hybridizes thereto.

5. A DNA sequence according to any of claims 1 to 3 which includes the 2482 bp SalI restriction fragment containing sequences 37781 to 40244 of Seq Id 1, or a sequence which hybridizes thereto.

6. A DNA sequence according to claim 1 which includes the sequence of Seq Id 1, or a sequence that hybridizes thereto.

7. A DNA sequence according to claim 1 which codes for an enzyme having an amino acid sequence as given in Seq Id 2.

8. A recombinant vector containing a DNA sequence as defined in any one of claims 1 to 7.

9. A recombinant vector according to claim 8 which has a restriction map as set out in any one of figures 2 to 5.

10. A host cell carrying a vector according to claim 8 or claim 9.

11. A process for the production of cyclosporin or a cyclosporin derivative, comprising cultivating a host cell according to claim 10 and causing the host cell to produce the cyclosporin or cyclosporin derivative.

12. A method for the production of a cyclosporin derivative, comprising altering the DNA sequence coding for cyclosporin synthetase so that the enzyme causes the production of the cyclosporin derivative, placing the altered DNA sequence in a vector, transforming a host cell with the vector, and causing the host cell to produce the cyclosporin derivative.

13. A method according to claim 11 in which the DNA sequence coding for cyclosporin synthetase is altered by changing the fragments that code for amino acid recognition units.

FIGURE 1

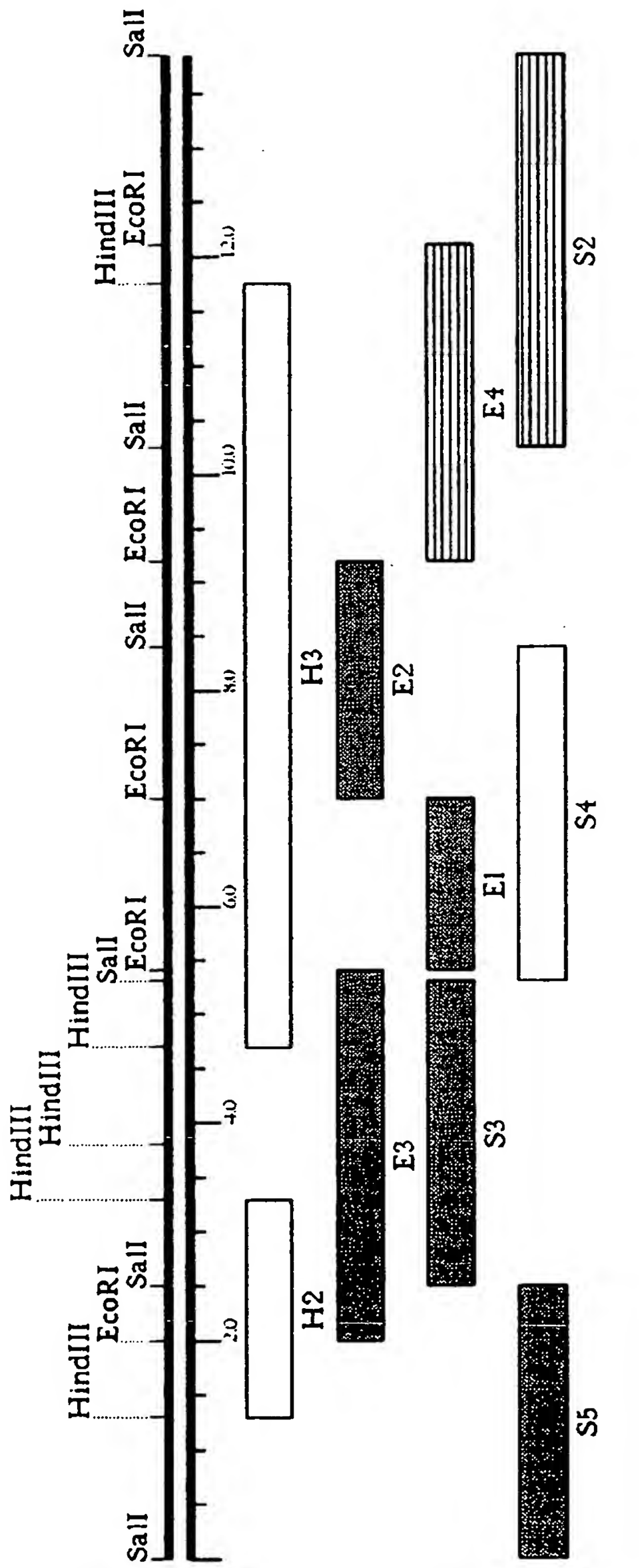

SalI
HindIII
EcoRI
SalI
EcoRI
SalI
EcoRI
HindIII
SalI
EcoRI
HindIII
SalI
H3
H2
E4
S2
E2
E1
S4
E3
S3
S5

FIGURE 2

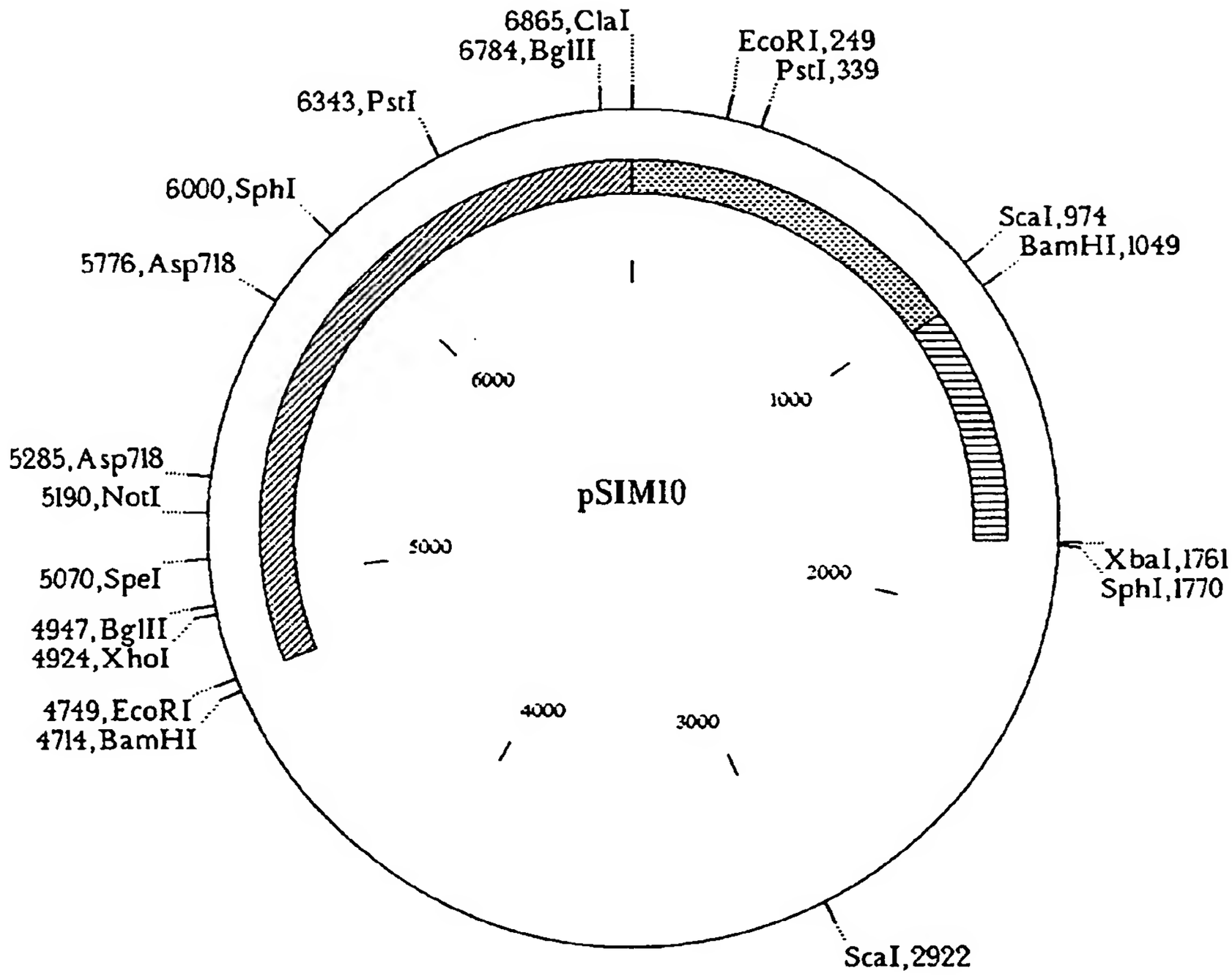

6865,ClaI
6784,BglII
EcoRI,249
PstI,339
6343,PstI
6000,SphI
ScaI,974
BamHI,1049
5776,Asp718
6000
1000
5285,Asp718
pSIM10
5190,NotI
5000
5070,SpeI
2000
XbaI,1761
SphI,1770
4947,BglII
4924,XhoI
4749,EcoRI
4714,BamHI
4000
3000
ScaI,2922

FIGURE 3

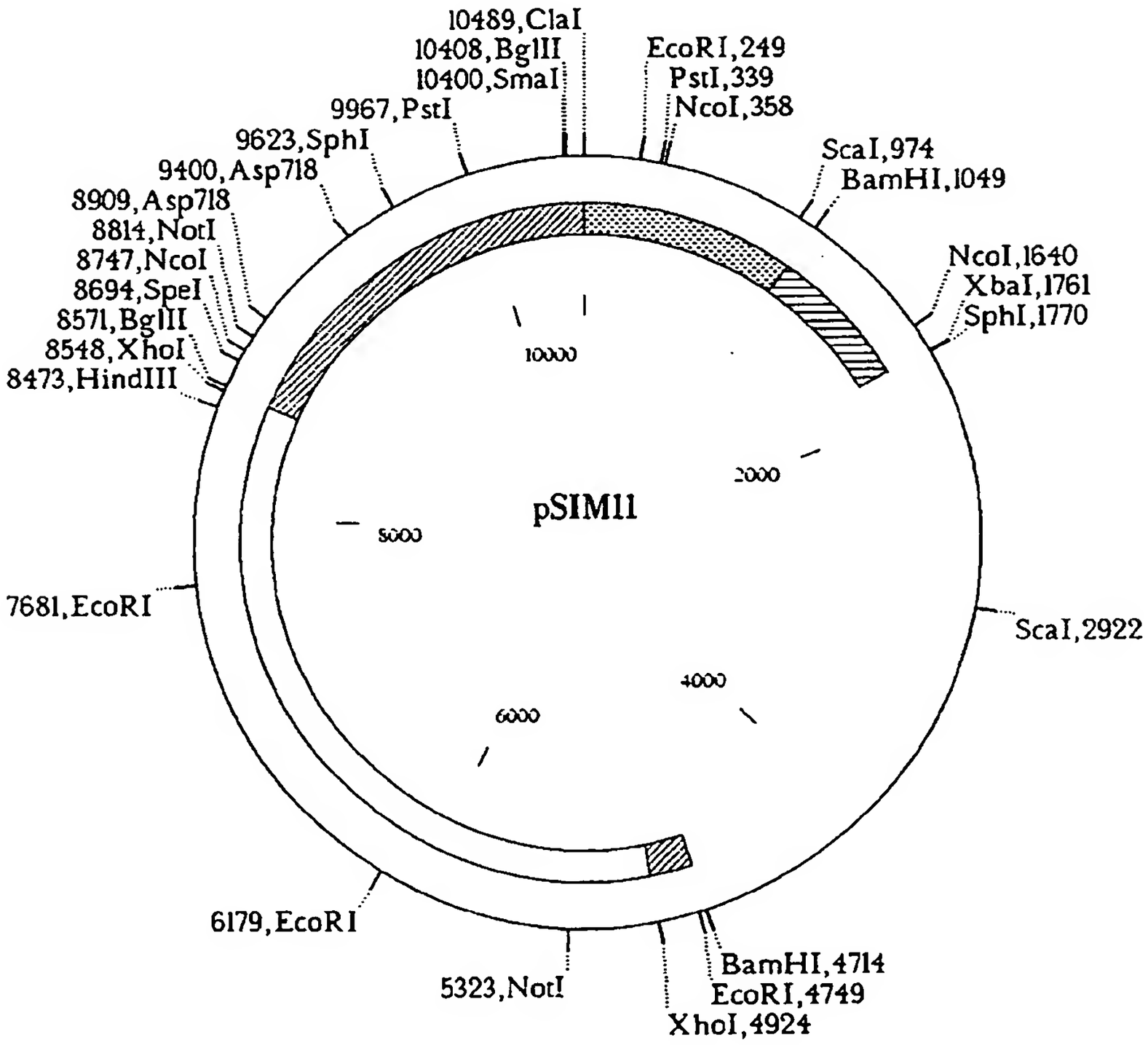

10489,ClaI
10408,BglII
10400,SmaI
EcoRI,249
PstI,339
NcoI,358
9967,PstI
9623,SphI
9400,Asp718
ScaI,974
BamHI,1049
8909,Asp718
8814,NotI
8747,NcoI
8694,SpeI
8571,BglII
8548,XhoI
8473,HindIII
NcoI,1640
XbaI,1761
SphI,1770
10000
2000
pSIM11
5000
7681,EcoRI
ScaI,2922
4000
6000
6179,EcoRI
5323,NotI
BamHI,4714
EcoRI,4749
XhoI,4924

FIGURE 4

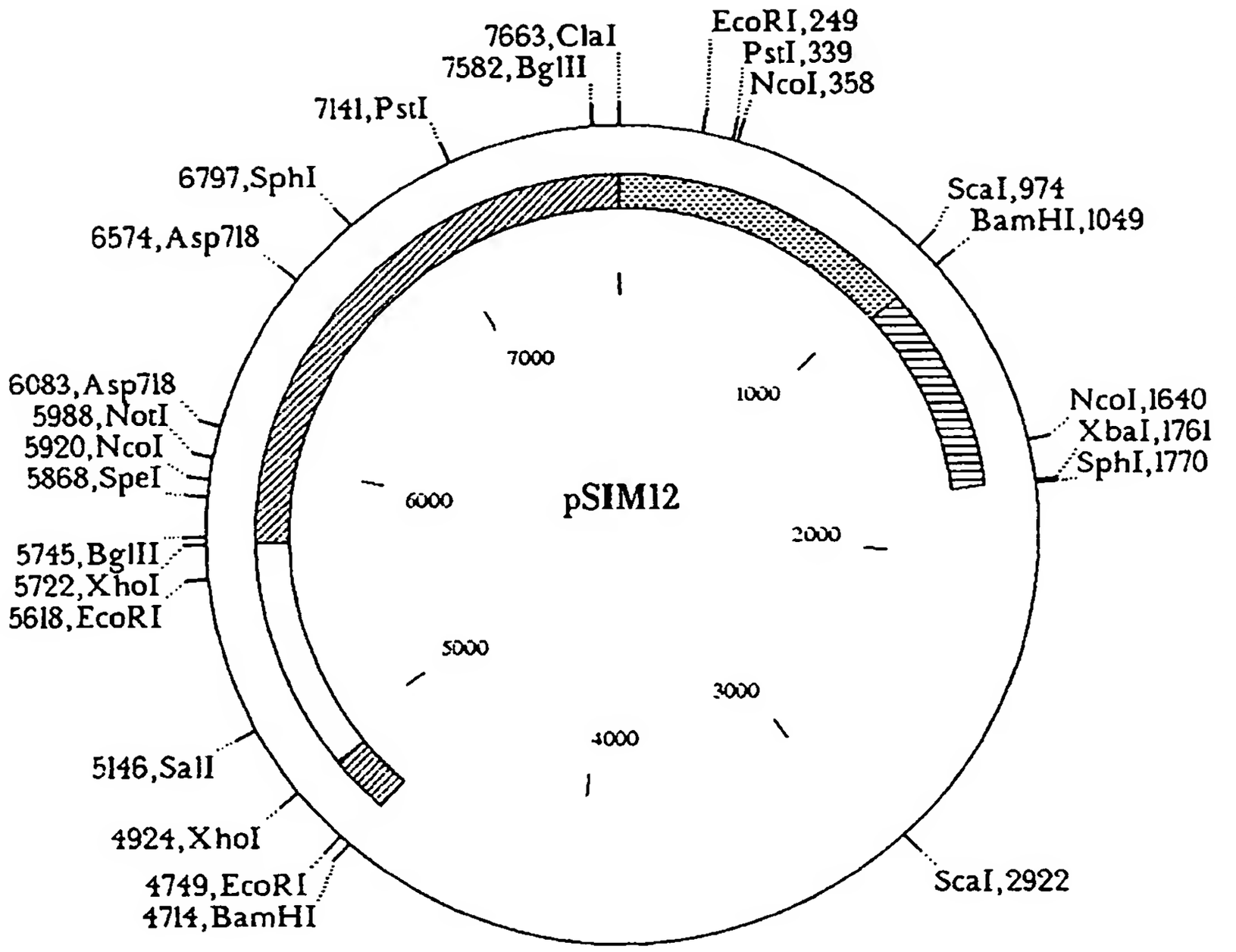
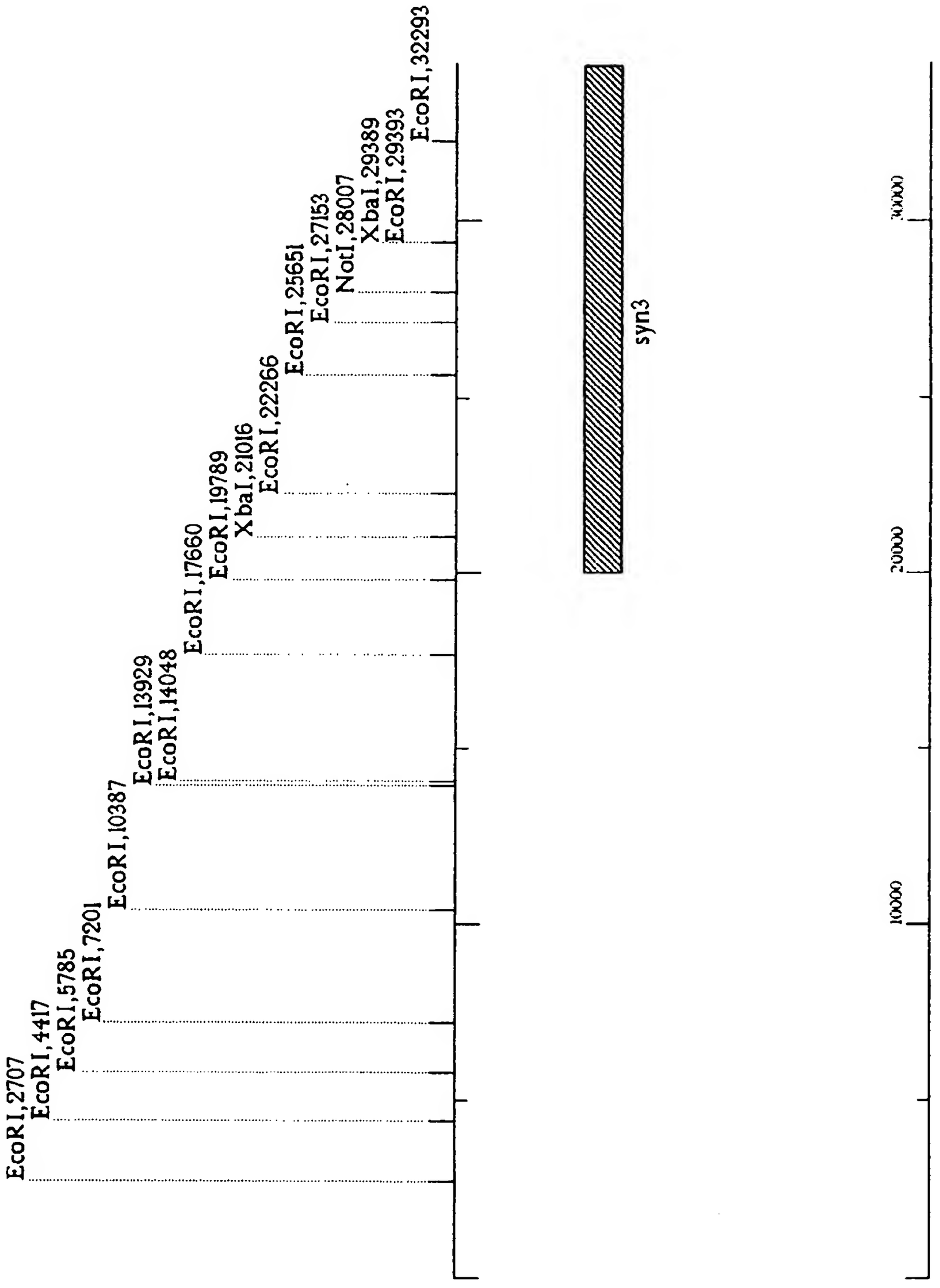

7663,ClaI
7582,BglII
7141,PstI
6797,SphI
6574,Asp718
6083,Asp718
5988,NotI
5920,NcoI
5868,SpeI
5745,BglII
5722,XhoI
5618,EcoRI
5146,SalI
4924,XhoI
4749,EcoRI
4714,BamHI
EcoRI,249
PstI,339
NcoI,358
ScaI,974
BamHI,1049
NcoI,1640
XbaI,1761
SphI,1770
ScaI,2922
pSIM12
1000
2000
3000
4000
5000
6000
7000

FIGURE 5


EcoRI,32293
XbaI,29389
EcoRI,29393
NotI,28007
EcoRI,27153
EcoRI,25651
EcoRI,22266
XbaI,21016
EcoRI,19789
EcoRI,17660
EcoRI,14048
EcoRI,13929
EcoRI,10387
EcoRI,7201
EcoRI,5785
EcoRI,4417
EcoRI,2707
syn3
30000
20000
10000